REFERENCE ONLY

UNIVERSITY OF LONDON THESIS

Degree PhD Year 2006 Name of Author HOSHI, N.

The Neuropharmacological, Cognitive and Mood Effects of ±3,4-Methylenedioxymethamphetamine (MDMA, 'ecstasy')

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Submitted for the degree of Doctor of Philosophy

University of London

April 2006

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Abstract

This thesis investigates the sub-acute and long-term neuropharmacological, cognitive and mood effects of ecstasy use. The first Positron Emission Tomography (PET) study used the ^{18}F-dopa ligand to assess presynaptic dopaminergic function in ex-ecstasy users, poly-drug controls and drug-naïve controls. Increased ^{18}F-dopa uptake was found in the putamen of ex-ecstasy users compared to controls. This could suggest a compensatory upregulation of the dopaminergic system. The second PET study used the ^{11C}DASB ligand to assess 5-HT transporter density in ex-ecstasy users, poly-drug controls and drug-naïve controls. No significant group differences indicated recovery of 5-HT transporter density following cessation of ecstasy use, replicating several very recent studies. Studies 3 and 4 assessed cognitive function and aggressive cognitive bias respectively in ex-ecstasy users, current ecstasy users, poly-drug controls and drug-naïve controls. A general tendency towards impaired learning and memory in all 3 drug using groups suggested that drug use in general rather than ecstasy use *per se* could be responsible. In addition, *recent* drug use was associated with poorer memory performance and impaired response inhibition. No group differences were observed in aggressive cognitive bias. However, Study 5, using the same task with over 100 participants showed increased aggressive interpretative bias (and increased self-rated aggression and depression) 4 days after acute ecstasy use. No evidence of gender differences was found. Study 6 built on findings with serotonergic challenges to explore transient 5-HT depletion. As predicted, on the night of ecstasy use participants showed subtly elevated fear recognition accuracy and the reverse 4 days later. In summary, evidence of recovery of serotonergic function following cessation of ecstasy use should be viewed alongside long-lasting alterations in dopaminergic function. Cognitive 'deficits' are less apparent when ecstasy users are matched with controls for use of all other recreational drugs. 'Mid-week' lowering of mood is now one of the most replicated findings within the ecstasy literature.

Acknowledgements

"Fantastic expectations, amazing revelations,
Final execution and resurrection,
Free expression as revolution,
Finding everything and realising.....you've got the fear"

Ian Brown

First and foremost I would like to thank my supervisor, Prof. Val Curran, whose continual support and kind encouragement has inspired me throughout the arduous process of completing this thesis. Her dedication to my work on both a practical and personal level has been an inspiration, and I feel truly lucky to have had her to guide me. There are also many other people have helped me through 'the fear' on countless occasions during the years of my PhD, I will always be grateful for their friendship: Matthew Bennett and Marc Sethi; Dr. Matthew Whalley, Dr. Robin Hayman, Lee Rowland (the Marlborough Army); and in particular Dr. Celia Morgan for nurturing my love of pastry based products and putting up with my office antics & Dr. Sally Zlotowitz for the years hilarity.

In addition, I would like to thank all at Hammersmith Hospital who collaborated with me: Prof. Paul Grasby, Dr. Paula Piccini, Dr. Yen Tai, Dr. Sudharkar Selvaraj, Dr. Zubin Bhagwagar, Dr. Catherine Brignell, Catherine Boundy and Lisa Cohen. Thanks also to Jat, Sachin, Hannah, Lu and Kate for their assistance with data collection, and of course to the many participants who took part in my research.

I would also like thank my family who have all played important parts in getting me through with my sanity intact: my brother Bijan, my sister Stella and brother in law Darren, and my beautiful nephews Gus and Vince. Finally, I would like to express my eternal gratitude to my Mum and Dad. Their love, encouragement and total confidence in me has coaxed me through my PhD. I couldn't have done it without them and I hope I always make them proud. Although it is but a small gesture in the face of all they have done for me, I dedicate this thesis to them.

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Selected Abbreviations and Acronyms

AADC	Aromatic amino acid decarboxylase
AQ	Aggression Questionnaire
ARS	Aggression Rating Scale
BDI	Beck Depression Inventory
BS	Barratt Impulsivity Scale
CSF	Cerebrospinal Fluid
DA	Dopamine
fMRI	Functional Magnetic Resonance Imagery
LSD	D-Lysergic acid diethylamide
MDMA	3,4-Methylenedioxymethamphetamine
MRS	Mood Rating Scale
NART	National Adult Reading Test
PET	Positron emission tomography
RMBT	Rivermead Behavioural Memory Test
RT	Reaction Time
RVIP	Rapid Visual Information Processing
SD	Standard deviation
SE	Standard error
SERT	Serotonin transporter
SOC	Stockings of Cambridge task
SPECT	Single photon emission computed tomography
SSRI	Selective serotonin reuptake inhibitors
STAI	State/Trait Anxiety Inventory
SWM	Spatial Working Memory task
TMT	Trail Making Test
TRP	L-tryptophan
5-HT	5-hydroxytryptamine, serotonin
5-HIAA	5-Hydroxyindoleacetic acid

Chapter 1 - Introduction

"Words are, of course, the most powerful drug known to mankind"

Rudyard Kipling

1.1 Historical Background

3,4-Methylenedioxymetamphetamine (MDMA) was first patented as a by-product in the synthesisation of a new medication in 1914 by the German pharmaceutical company Merck (Holland, 1999). There is little mention of MDMA until it resurfaced in 1976 when Alexander Shulgin (the self-proclaimed 'Godfather of Ecstasy') synthesised it and tried it along with his wife and their friends. Among these friends were psychotherapists who saw the enhanced mood and empathy induced by taking MDMA as a possibly useful adjunct to psychotherapy. For several years, small groups of therapists practised the use of MDMA, described by its advocates as 'penicillin for the soul' (Saunders, 1997). Although these sessions are claimed to have been 'highly successful', the underground nature of the practice led to a lack of meaningful results on therapy outcome.

At the same time, the recreational use of MDMA had started to escalate. It was becoming popular in bars in the US, and in some places in Texas it was available over the counter. Ecstasy, MDMA's street name, allegedly comes from a dealer at the time: "Ecstasy was chosen for obvious reasons, because it would sell better than calling it Empathy. Empathy would be more appropriate, but how many people know what it means?" (Holland, 1999). However, the so-called 'golden years of Ecstasy' (Saunders & Doblin, 1996) ended in 1985 when the Drug Enforcement Agency in America, having become aware of the increasing recreational use of MDMA, placed it in schedule 1.

MDMA was made illicit in the UK in 1977, before its widespread recreational use began. Ecstasy began to filter into the UK from the holiday island of Ibiza in the mid-eighties, where the dance music scene was beginning to take off. 1988 became

known as the 'summer of love', as large-scale dance parties began to happen across the country, and ecstasy use was synonymous with these parties. It was the beginning of what has been described as "the most spectacular youth movement of the century" (Collin, 1997).

1.2 Patterns of recreational ecstasy use

"Drug users are no longer a mad, bad or immoral minority. Using drugs is normal for the chemical generation, and the drug that defines them is ecstasy" (Hammersley et al., 2002)

Estimating recreational drug use is notoriously difficult, as users do not regularly present at hospitals, drug clinics or other places for help. For the large part, they continue with their normal lives never coming into contact with the authorities. In 1995, reported estimates of ecstasy use in the UK ranges from 500,000 (Saunders, 1995) to 750,000 (Cook, 1995) tablets consumed every weekend. Holland (1999) claims that it was an accepted figure by the British government that ecstasy use had increased by 4000% between 1990 & 1995. An estimated 1.8% of 16-59 year olds report having used ecstasy in the last year (Roe, 2005), although this increases to 4.8% when just looking at young adults (16-24 years old). An estimated 2% of 11-16 year olds in England had taken ecstasy in the last month in 2000 (Blenkinsop et al., 2001). These figures are higher than other countries in Europe where ecstasy use is as low as 0.2% (2005 Annual Report on the State of the Drugs Problem in the European Union, EMCDDA, 2005). Roughly 556,000 16-59 year olds in the UK have taken ecstasy in the last year, and 213,000 in the last month. Although there was a steady increase in ecstasy use from 1996 to 2001, then a slight decrease from 2001-2002 until the present, the report from the most recent British Crime Survey (2004/2005) suggests the actually figures have remained fairly stable since 1998 (Roe, 2005). It is also reported to be the easiest drug to obtain after cannabis (Condon & Smith, 2003).

However, these numbers rise dramatically when looking at people who attend dance events, where ecstasy appears to be an integral part of the culture. Van de

Wijngaart et al. (1999) carried out a large-scale investigation at dance parties in the Netherlands. In this population they found that 81% of attendees interviewed had tried ecstasy, and that 64% has taken it that night; 41% and 34% of people had used cannabis and amphetamines on the night of interview. Poly-drug use is common among ecstasy users, with the majority reporting usage of other recreational drugs. Parrott et al. (2001) found that those who use ecstasy tend to use many other recreational drugs, and that frequency of use of different recreational drugs increases in parallel. For example, in a group of 119 heavy ecstasy users, 91% used cannabis, 83% amphetamines, 80% cocaine and 81% LSD. Users also report using drugs in combination with ecstasy. Verheyden et al. (2003a) reported that only 0.7% of 422 ecstasy users reported *never* using ecstasy conjointly with any other drug, while 59% reported *always* using it with another drug (although this did include tobacco and alcohol). Winstock et al. (2001) reported the findings from 1151 questionnaires distributed in the UK dance music magazine, Mixmag. 88% of respondents reported using alcohol, 93% amphetamines, 82% cannabis and 58% cocaine in combination with ecstasy. They also reported the use of other drugs to assist in reducing the 'come-down' associated with the drug: 60% alcohol, 82% cannabis and 18% benzodiazepines. An alarming result from this study was that 70% of those who had used ecstasy scored within the harmful drinking range on the Alcohol Use Disorders Identification Test. However, it is important to remember that this population was self selected, and that little information about life history could be obtained, thus it is possible that the group is not representative of the wider population of ecstasy users. As no control group who did not use illicit drugs was investigated, it may also be possible that this is a trend apparent within this age group regardless of whether or not they use ecstasy. Although these findings supported those of the British Crime Survey (2003/4) that prevalence of ecstasy use seemed to have reduced slightly, they also found that the prevalence of heavy ecstasy use (>4 pills per session) had almost doubled. In addition, 16.4% of 16-24 year old ecstasy users report frequent use, defined as greater than once per month (Roe, 2005).

Collin (1997) describes ecstasy, in combination with dance music, as the driving force behind one of the biggest youth movements in Britain. The figures above indicate that this phenomenon shows little sign of slowing down, and that ecstasy

use within the dance scene is, in fact, increasing in terms of dosage and frequency of use.

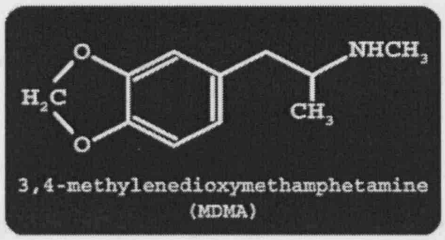
1.3 Summary

The figures outlined above clearly demonstrate the necessity of research into the effects of MDMA. Public health information such as that relating to the effects of recreational drugs should be directly derived from empirical scientific research which is then disseminated in a clear and concise way. As many young people expose themselves to MDMA in the form of ecstasy tablets on a regular basis it is essential that clear and accurate information is available to help people make informed choices in relation to their behaviours.

In the following literature review, I will initially discuss the pharmacology of MDMA and serotonergic function in humans, with particular emphasis on serotonin's role in depression, aggression and impulsivity. I will then review the pre-clinical literature relating to the long-term effects of MDMA and discuss the relevance of this large body of work to the debate about the possibility of MDMA-induced neurotoxicity in recreational ecstasy users. The acute, sub-acute and long-term effects of MDMA on cognitive function and mood in humans will then be discussed, alongside methodological problems endemic to this type of research.

While MDMA is the major psychoactive compound in ecstasy tablets, through out this thesis I will refer to the effects of 'MDMA' when discussing controlled laboratory based investigations of MDMA administration. When discussing investigations of recreational users where there can be no control or certainty over the amount of MDMA ingested, I will use the term 'ecstasy'.

1.4 The pharmacology of MDMA



3,4-Methylenedioxymetamphetamine (MDMA) is a synthetic amphetamine derivative. It is a ring-substituted amphetamine, its structure being similar to both amphetamine and the hallucinogen mescaline. Unlike other stimulant drugs, which act mainly through the dopaminergic and noradrenergic systems, MDMA's main action is on serotonin (5-HT). MDMA binds to serotonin transporters, and due to its size can be taken into the presynaptic cell. This allows it to stimulate the release of 5-HT, as well as preventing its reuptake. Thus, MDMA causes large amounts of 5-HT to flood the synapse. MDMA leads to a subsequent, temporary depletion of 5-HT as tryptophan hydroxylase, the enzyme required to synthesise 5-HT, is inactivated. To a lesser extent, MDMA also causes the release of dopamine and noradrenaline. The release of dopamine, however, seems to be dependent on the release of 5-HT as pretreatment with fluoxetine (which blocks 5-HT transporters, and thus prevents MDMA entering the cell and releasing 5-HT) inhibits the usual dopamine release (Koch & Galloway, 1997).

Studies of MDMA administration in humans have found that the drug has non-linear pharmacokinetics (de la Torre et al., 2000a). This indicates that plasma concentrations of MDMA do not increase in a dose-dependant manner, and that small increases in dose could lead to disproportionate increase in plasma concentrations of the drug. This has implications for recreational users who may think they are increasing their dose only slightly, while actually considerably increasing the risks associated with higher dosage (for example neurotoxicity).

MDMA's unique pharmacological and subjective effects compared to both stimulants and hallucinogens has prompted some to argue that it should be placed in

a new pharmacological class, called 'entactogens', from the Greek meaning 'touching within' (Nichols, 1986).

1.5 Serotonergic function in humans

Serotonin (5-hydroxytryptamine, 5-HT) is a major neurotransmitter that has been implicated in the control of a wide range of behaviours. 5-HT is stored in vesicles within the nerve terminal and its synthesis is started by tryptophan hydroxylase, an enzyme located in serotonergic neurons. Neuronal firing causes the release of 5-HT, after which it either binds to receptors or is transported back into the nerve terminal by a reuptake mechanism.

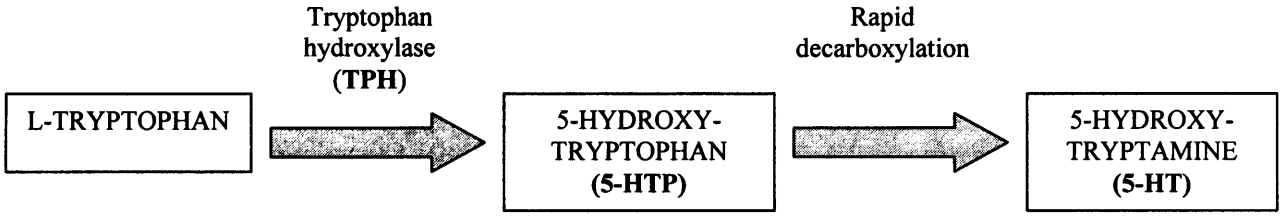


Figure 1.1: Synthesis of serotonin

5-HT neurons are located primarily in the Raphe Nucleus, located in the brain stem area. These cell bodies give rise to many pathways that innervate large areas of the brain and spinal cord. This wide ranging innervation could account for the many different behaviours thought to be affected by variations in the serotonergic system, including depression, aggression, sleep, cognitive function, appetite, sexual behaviours and circadian rhythm. There is a strong possibility that an interrelationship exists between these factors; for example alterations in cognitive function, sleep patterns and appetite are all common features of depression. However, in the following sections I shall discuss the role of serotonin in depression, aggression, impulsivity and cognitive function separately.

1.5.1 Serotonin and depression

The serotonin hypothesis of depression implies that variations in the serotonergic system may lead to a vulnerability to depression. Although a wide range of supporting evidence exists, the precise nature of its role in the pathology of depression is unclear (Maes & Meltzer, 1995).

Different methods have been used to demonstrate the existence of a link between serotonergic function and depression. As 5-HT cannot cross the blood brain barrier, tryptophan (TRP, the precursor of 5-HT) depletion is used as an indirect way of manipulating brain 5-HT synthesis. Administering a TRP-free amino acid drink to healthy male volunteers was found to reduce plasma tryptophan by almost 80% (Young et al., 1985). As cerebrospinal fluid (CSF) sampling of 5-hydroxyindoleacetic acid (5-HIAA, the metabolite of 5-HT) during tryptophan depletion has demonstrated a correlation between plasma tryptophan and levels of 5-HIAA (Williams et al., 1999), it has been assumed that this corresponds with a fall in brain 5-HT.

Delgado et al. (1991) used Young et al.'s (1985) method of tryptophan depletion to investigate serotonergic function in depressed individuals. Administration of a TRP-free amino acid drink was found to induce relapse of depressive symptoms in participants being successfully treated with Selective Serotonin Reuptake Inhibitors (SSRIs, the 'new generation' of anti-depressants that block the reuptake of 5-HT). Booj et al. (2005) also found relapse in a similar population, and observed that the effect was more pronounced in women than in men. A lowering of mood has been observed with non-depressed men with a family history of depression (Benkelfat et al., 1994). No effect on mood is seen in healthy participants with no family history of depression (e.g. Shansis et al., 2000) indicating a genetic risk factor.

Neuroendocrine challenges have also been administered to depressed patients to explore the relationship between 5-HT and depression. Cleare et al. (1998) administered 30mg of d-fenfluramine (a 5-HT releaser) to patients with unipolar major depression. A correlation was found between cortisol response to the d-

fenfluramine and several depression scales. Furthermore, cortisol response to the drug was found to be a predictor of good response to antidepressants in the future.

Other studies have found that baseline l-tryptophan availability is a factor in predicting response to anti-depressant treatment (Porter et al., 2003). Blunted cortisol response to the 5-HT agonist ipsaprione (Riedel et al., 2002a) and low levels of CSF 5-HIAA (van Praag, 1982) have also been found in depressed patients.

1.5.2 Serotonin and aggression

The serotonergic system has also been implicated in aggressive behaviour. Placidi et al. (2001) investigated depressed patients who had attempted suicide and found that those with low CSF 5-HIAA had used more violent means of attempting suicide, suggesting that low serotonergic activity may indicate a predisposition to more aggressive suicide attempts. It has been claimed that this type of violent behaviour towards oneself, and violent behaviour towards others, are manifestations of underlying aggressive tendencies (Feldman et al., 1997).

Fenfluramine challenges and TRP depletion have also been used to demonstrate an association between 5-HT function and aggression. Coccaro et al. (1997) found that PRL response to d-fenfluramine challenge correlated with aggression ratings in males with personality disorders. This relationship is not confined to patient groups: Wingrove et al. (1999) found that plasma tryptophan correlated positively with aspects of the Buss-Durkee Hostility Inventory (BDHI) in healthy male volunteers. Bjork et al. (2000) found that aggression was increased after TRP-depletion only in men with high baseline levels of aggression compared to those with low base line aggression. Bond et al. (2001) also showed that TRP-depletion increased aggression in women during the pre-menstrual phase of their cycle.

1.5.3 Serotonin and impulsivity

Impulsivity is a common element in many aggressive behaviours and, like aggression, it has been linked to 5-HT function. Lucki (1998) describes dysfunction of impulse control, which is related to impaired serotonergic function, as being part of the 'biology of aggression'. Dolan et al. (2001) found that 5-HT function (as measured by prolactin response to fenfluramine) had a stronger inverse correlation with impulsivity than with aggression in male offenders with personality disorders. Paroxetine (an SSRI) reduced both aggression and impulsivity in males with a history of criminal behaviour (Cherek et al., 2002). Two studies by the same group have found evidence of lower levels of plasma (Spreux-Varoquaux et al., 2001) and cerebrospinal fluid (Cremniter et al., 1999) concentrations of 5-HIAA in impulsive compared to non-impulsive suicide attempters. Although impulsivity, aggression and 5-HT function are often investigated together, there is also evidence that impulsivity is influenced by serotonergic function independently, in the absence of aggressive behaviour. Walderhaug et al. (2002) found that lowering serotonin in healthy male volunteers (with no history of aggressive behaviour) using rapid TRP depletion led to increased impulsive (disinhibited) responses on a Continuous Performance Test. Clark et al. (2005), however, found contradictory results. Tryptophan depletion did not significantly alter performance on the Stop Signal task in healthy male and female volunteers.

1.5.4 Serotonin and cognitive function

Although serotonin is often linked to cognitive function, evidence to support this link is conflicting. Park et al. (1994) administered a battery of cognitive tests to male volunteers following TRP depletion. The main effect of TRP depletion was on learning, demonstrated by the increased number of errors and greater number of trials needed to learn associations in a visual paired associates task. Visual discrimination was also affected, but on tests of executive function (such as the Tower of London test and a card sorting task) performance was unimpaired. Thus, the authors concluded that the serotonergic system plays a specific role in memory and learning rather than being implicated in frontal lobe function. Riedel et al.

(1999) followed a similar procedure and also found evidence that they argued reflected diminished memory consolidation after TRP-depletion. However, Coull et al. (1995) found some improvement in speed of response following TRP-depletion, Shansis et al. (2000) found no effect on memory or attention, and Schmitt et al. (2000) found that focused attention was improved. Schmitt et al. (2000) explained some of the conflicting results by pointing out that the time of test administration varied between studies. They showed that, in agreement with Riedel et al. (1999), memory is affected when learning is carried out 5-6 hours after TRP depletion, when the amino acid drink has affected central 5-HT. When the learning phase was administered only 30 minutes post TRP depletion (prior to any effect of the drink), there is no evidence of memory disturbances at the recall phase hours later. They conclude that TRP-depletion affects encoding rather than retrieval of memory. Shansis et al. (2000) explain their lack of findings as being due to the lack of sensitivity of the tests used in comparison to those used by Riedel et al. (1999). Murphy et al. (2002) discus the effect of familiarity with the task, suggesting that this is a factor in determining whether impairment is seen after TRP depletion or not. It is apparent, therefore, that inconsistencies in findings in TRP depletion studies of cognitive function could be due to the differences in methodologies used (Reilly et al., 1997).

More recently studies have found an effect of TRP depletion on processing of affective stimuli. Murphy et al. (2002) found that TRP depletion increased response times for happy targets in an affective Go/No go task, while no difference was seen for sad targets. Harmer et al. (2003b) carried out a facial expressions recognition task after TRP depletion. Recognition of fearful facial expressions (but not other basic emotions) was significantly impaired only in female participants. This discrepancy between male and female participants could be a factor in explaining the variability in the results of TRP depletion studies. Females only were tested on facial expression recognition following TRP augmentation (using nutritionally sourced tryptophan), and showed increased efficiency in recognition of fearful expressions.

1.6 Pre-clinical Studies

Studies investigating the effects of MDMA in animals have been carried out since the mid-1980s, and have consistently found three types of changes in animal brains following MDMA administration: reductions in 5-HT and 5-HIAA (5-hydroxyindoleacetic acid, the metabolite of 5-HT), decreases in the activity of tryptophan hydroxylase (the enzyme that begins the synthesis of 5-HT) and lower density of 5-HT reuptake sites, or transporters (see Ricaurte et al., 2000, for review). These studies typically use a regime of twice daily subcutaneous drug administration over a period of 4 days. These effects have been demonstrated in many species including rats, guinea pigs and several species of non-human primates. Although the cell bodies appear to be spared, MDMA damages the serotonin nerve axon terminals. Regeneration of 5-HT axon terminals does seem to occur, although the time course and extent of recovery varies across species. The evidence indicates that recovery is much greater, and occurs over a much shorter time period, in rats than in non-human primates. Battaglia et al. (1988) found that these neurotoxic effects in rats are evident up to 12 months after administering 20 mg/kg of MDMA twice daily for 4 days. There was, however, almost full recovery of 5-HT uptake sites in some brain areas, even following a 90% loss. Hatzidimitriou et al. (1999) found that squirrel monkeys who had received 5 mg/kg of MDMA twice a day for four consecutive days still showed 5-HT deficits 7 years later. There was, however, evidence of recovery in some brain areas (e.g. the hypothalamus). This finding supports evidence of other studies indicating regional differences in the neurotoxic effects of MDMA (Morgan, 2000). Longer lasting degeneration of serotonergic axons has been found in areas of the forebrain including the hippocampus and neocortex. There is little evidence for recovery in these areas. Scheffel et al. (1998) used positron emission tomography (PET) to investigate recovery from the neurotoxic effects of MDMA in baboons after administering 5mg/kg twice daily for 4 days. The results of PET scans carried out at 9 and 13 months after administration support the notion of regional differences as the baboons showed increases in 5-HT in some (e.g. hypothalamus) but not other (e.g. neocortex) brain areas. Some brain areas show an over compensation in axonal regrowth, termed 'a pruning effect'. Interestingly, MDMA seems to be selective in its effects; it damages the serotonergic system but generally shows no

evidence of long-term effects on any other monoaminergic system (Ricaurte et al., 2000). Although there has been a recent debate about the effects of MDMA on the dopaminergic system (see Chapter 2), at present the only species known to show dopaminergic neurotoxicity following MDMA administration is mice (see Colado et al., 2004, for review).

1.6.1 Serotonergic neurotoxicity in animals: a model for human ecstasy users?

This wealth of pre-clinical data showing that MDMA is neurotoxic to many species of animals has lead to the debate concerning the possibility that repeated MDMA use may lead to degeneration of 5-HT neurons in humans. There are, however, several areas of controversy surrounding this claim.

It has been argued that the route and schedule of drug administration in animal studies bears no resemblance to the way recreational ecstasy users take the drug. Humans take MDMA orally and generally once or twice a weekend, very differently to the accepted animal regime of high doses administered subcutaneuously, twice daily over four days. Although Ricaurte et al. (2000) argue that some users take up to 10 doses per night, this is highly unrepresentative of the general recreational ecstasy using population, and is even more unlikely to occur on four consecutive days. Ricaurte et al. (1988a) administered 5mg/kg of MDMA twice daily for four days to 9 squirrel monkeys. Three of the monkeys received the drug orally, three subcutaneously and three were injected with an equivalent volume of liquid as a control group. Depletion of serotonin in the brain was evident for both routes of administration of active drug, but to a much lesser extent after oral administration. For example, in the frontal cortex oral doses depleted serotonin by 42% compared to 75% depletion after subcutaneous administration. In the caudate nucleus, oral doses led to 29% depletion, considerably lower than the 86% reduction caused by injecting the drug. Thus, it is apparent that much of the animal research could lead to an overestimation of the damage caused to the serotonergic system by MDMA. However, there are again inter-species differences as Finnegan et al. (1988) used the same design with rats and found no differences in serotonin depletion between subcutaneous and oral administration.

Another area of debate regarding the relevance of animal research to the human model of MDMA neurotoxicity is the dosage administered to the animals. It is necessary to administer 20 mg/kg of MDMA to rats twice daily over four days to find evidence of neurotoxicity, and the lowest dose found to cause neurotoxicity in monkeys is 5mg/kg. Recreational ecstasy users usually take about 1-2 mg/kg orally. Many researchers argue that smaller animals required higher doses of a drug to achieve equivalent effects (Ricaurte et al., 2000), a notion that can be translated into an equation for 'inter species scaling' (Chappell & Mordenti, 1991), taking into account body mass and surface area. Ricaurte et al., (2000) argue that using this principle, it becomes apparent that human doses lie within the range of those tested on animals. The principle of interspecies drug dose scaling is, however, far from clear. Grob (2000) argues that the notion fails to take factors such as interspecies differences in pharmacokinetics and drug metabolism in to account. He points out that although it may be a reasonable 'rule of thumb', it is by no means applicable to every drug. He cites the example of the drug fenfluramine. Humans metabolise fenfluramine in a way that is much more similar to small species like rats than to monkeys, and thus they are less likely to be affected by its neurotoxicity than monkeys. This is particularly pertinent to the current debate when one considers the fact that fenfluramine and MDMA have very similar pharmacological actions.

A more fundamental debate in this area questions the classification of a neurotoxin. Ricaurte et al. (1988b) reported finding neurotoxic effects in non-human primates after a single 5mg/kg dose of MDMA. However, Lieberman & Aghajanian (1999) point out that the data reveal that there was a reduction of 5-HT in the thalamus and hypothalamus, but no change in any other area. They argue that this is not a sufficient change to assert that neurotoxic effects were observed. Grob (2000) points out that reductions of 5-HT and its metabolites are not enough evidence to label a substance neurotoxic, as these levels can be reduced with no damage to the neurons. O'Callaghan & Miller (1993) suggest that to classify a substance a neurotoxic, it is necessary to have validated biological measures of damage to cell bodies. One measure they propose is the presence of reactive gliosis, which occurs after nervous system damage. This is not present after MDMA administration. This is, however, still a contentious area. Increases in glial fibrillary acidic protein

(GFAP), a marker of neurotoxicity, were not observed in rats until twice daily administrations of high doses (75-150mg) of MDMA were given over two days (O'Callaghan & Miller, 1993), although large decreases in 5-HT were apparent following twice daily administrations of 5-30mg/kg. O'Callaghan & Miller (2001) maintain that this is simply evidence for a "down-regulation" of the serotonergic system, rather than an expression of neurotoxicity, whereas others claim the techniques are insensitive to serotonin neurotoxicity (Wilson & Molliver, 1994). A finding that could cause concern in relation to human users is that serotonin neurotoxicity is increased in animals by high ambient temperatures (Huether et al., 1997). Thus, it has been suggested that human users who take MDMA repeatedly through out the night, in hot nightclubs could be at increased risk of damaging their serotonergic system (Parrott, 2004b).

1.6.2 Functional consequences of MDMA induced neurotoxicity

Although evidence of reductions of 5-HT and damage to nerve terminals has consistently been found in many species of animals, an equally consistent finding is that there is no alterations in the behaviour of these animals (for review, see Green et al., 2003). For example, Taffe et al. (2001) found that no behavioural differences were found between rhesus monkeys with over 50% reduction of CSF 5-HIAA caused by MDMA administration and control animals. However, a small number of studies do report some minor behavioural changes. Marston et al. (1999) administered a delayed non-match to place test to rats who had been administered twice daily ascending doses of MDMA (10, 15, 20 mg/kg). Although the authors report impaired learning 16 days after drug administration, in fact the results indicated that at the most difficult level of the task (the longest delay between learning and response) the MDMA group failed to show the same degree of improvement demonstrated by the control group. Mechan et al. (2002) found less anxious behaviours in rats treated with 12.5mg/kg MDMA compared to control animals in the elevated plus maze. Taffe et al. (2002) attempted to assess whether any behavioural differences could be found in cognitive ability during serotonergic challenges. MDMA-treated and non-treated (control) rhesus monkeys were given ketanserin (a 5-HT antagonist), mCPP and hydrobromide (both 5-HT agonists).

The monkeys' performance on various cognitive tests was investigated under each drug condition, and the authors hypothesised that the MDMA-treated monkeys' behaviour would be more sensitive to disruption by these compounds, as a result of some disruption of the 5-HT system caused by previous MDMA exposure. Although they found that the MDMA-treated monkeys had 76-93% reductions of 5-HT in the neocortex, the behavioural responses of the two groups overlapped substantially. The MDMA-treated animals showed a trend towards increased sensitivity to mCCP and hydrobromide on tests of sustained attention, reinforcer efficacy and response speed, although only one aspect of a reaction time task showed significant differences to the control group after mCCP treatment. This study demonstrates that even if behavioural differences are not apparent under normal circumstances, minor behavioural alterations can be seen under conditions that challenge the serotonergic system. However, given the large number of tests (that were also split into a series of sub-tests) that were administered, and the fact that only reaction time (RT) on one measure was found to be significantly different, there is clearly a risk that this finding may reflect a type I error.

The lack of functional consequences in animals exposed to MDMA is an interesting phenomenon when considering the range of cognitive deficits and psychiatric problems reported in human ecstasy users that are regularly attributed to altered functioning of the serotonergic system caused by MDMA exposure. Yet high levels of 5-HT depletion appear to have no functional consequences in animals. That some changes in behaviour have been seen under serotonergic challenges suggests some neurochemical change that does not directly affect behaviour. In light of these observations, Cole et al. (2002c) claim that "simplistic theories based on MDMA-induced neurotoxicity are inadequate" in explaining apparent functional consequences of ecstasy use in humans.

1.6.3 Summary

Three types of changes have been repeatedly identified in animal brains following MDMA administration (i) reductions in 5-HT and 5-HIAA, decreased tryptophan hydroxylase activity and reduced 5-HT transporter density. However, whether this

truly reflects neurotoxicity or not has been debated as there is no evidence of cell death. Changes in 5-HT function appear to be long-lasting, with alterations in 5-HT function apparent in primates 7 years after MDMA administration (Hatzidimitriou et al., 1999). There does, however, appear to be regional differences in recovery, with some brain areas showing full recovery over time. There is little evidence of long-term changes to any other monoamine system, although recent investigations have focused on MDMA's affects on dopamine (see Chapter 2). Pre-clinical research has led to the suggestion that MDMA could also be neurotoxic in humans. There are, however, several caveats relating to the methodologies of animal research that limit its relevance to human research (e.g. dose regimes, method of drug administration). Interestingly, there appears to be little evidence of behavioural changes following neurotoxic MDMA administration in animals, which is particularly surprising given the broad range of behavioural changes in humans attributed to MDMA use.

1.7 Human Literature – Controlled Investigations of MDMA

1.7.1 Acute subjective and physiological effects of MDMA

Controlled laboratory based studies of the acute effects of MDMA are limited due to ethical considerations and the scheduled status of the drug. Authors report that generally participants complete these experiments without experiencing physical or psychological stress (Grob et al., 1996). Although one study reports a subject that had to drop out after one session complaining of anxiety, it was later established that he had been administered a placebo (Grob et al., 1996). In fact, most studies of the acute effects of MDMA report a general increase in positive mood, as would be expected from such a popular recreational drug.

The onset of the effects of MDMA are experienced approximately 30 –60 minutes after ingestion of the drug (Liechti et al., 2001a; Vollenweider et al., 1999), with the peak effects being experienced 90-120 minutes after ingestion (Cami et al., 2000; Hernandez-Lopez et al., 2002; Liechti et al., 2001b). These effects last for approximately 2–5 hours (see Table 1.1).

Authors	Subjects				MDMA Dose	Onset	Peak	Duration
	total	male	female	age				
Grob et al. (1996)	6	*	*	*	0.25-1 mg/kg	*	*	*
Vollenweider et al. (1998)	13	10	3	23 – 49	1.7 mg/kg	*	75-120 mins	*
Vollenweider et al. (1999)	13	10	3	23 - 47	1.7 mg/kg	Approx. 30 mins	Approx. 60 mins	1-2 hrs
Cami et al. (2000)	8	8	0	26.5 21 - 30	125mg & 75mg	*	90-120 mins	4 hrs
Liechti et al. (2000a)	16	12	4	27.4 +/- 4.4	1.5 mg/kg	20-120 mins	30 mins after onset	3 hrs
Liechti et al. (2000b)	14	13	1	26 21 – 41	1.5 mg/kg	60 mins	*	3.5 hrs
Gamma et al. (2000)	16	10	6	26	1.7 mg/kg	*	*	4 hrs
Liechti & Vollenweider (2000)	16	12	4	27.4 +/- 4.4	1.5mg/kg	Approx. 45 mins	*	3-5 hrs
Liechti et al. (2001a)	74	54	20	27 20 – 49	70 –150 mg (1.35 – 1.8 mg/kg)	30-60 mins	75-120 mins	3.5 hrs
Liechti et al. (2001b)	44	34	10	21 - 41	1.5 mg/kg (70 – 120 mg)	45-60 mins	90-120 mins	3.5 hrs
Harris et al. (2002)	8	5	3	24 - 39	0.5mg/kg, 1.5mg/kg	*	Approx. 120 mins	*
Hernandez-Lopez et al. (2002)	9	9	0	19-36	100mg	Approx. 45 mins	60-120 mins	4 hrs
Tancer & Johanson (2003)	12	6	6	18-31	1mg/kg, 2mg/kg	*	1-3 hours	*

Table 1.1: Time course of acute subjective effects – placebo controlled crossover designs

Recently, laboratory based, double-blind placebo controlled studies have been carried out, providing more accurate insights into the acute physiological and subjective effects of MDMA. The acute psychological/mood effects of MDMA include euphoria, increased sense of well being, self confidence, extroversion, thoughtfulness, emotional excitability and a general heightening of mood (Cami et al., 2000; Vollenweider et al., 1998). Evidence has also been found of the 'trade-mark' subjective effects of MDMA after a 1.5mg/kg dose: feeling of love for others, insightfulness, liking having people around and being at peace with the world (Harris et al., 2002). These are accompanied by mild depersonalization and derealization, and negative effects such as difficulty concentration, jaw clenching, thirst, lack of appetite and impaired gait. The Maddox wing devise has been used to demonstrate these effects of altered balance; increased muscle tension has been found in participants who had been administered 100mg (Farre et al., 2004; Hernandez-Lopez et al., 2002) and 125 mg of MDMA, but not after 75mg (Cami et al., 2000). De la Torre et al. (2000b) found a similar pattern with doses from 75mg upwards and noted that this pattern of effects is the opposite of that caused by sedatives, which produce muscle relaxation. Although MDMA does not cause hallucinations, higher doses have been shown to cause changes in perception of shapes and light, and feelings of heightened sensory awareness (Cami et al., 2000).

Vollenweider et al. (1999) examined the effect of MDMA on Prepulse Inhibition (PPI) of acoustic startle in both rats and humans. This is the reduction in the startle response when an acoustic stimulus is preceded by a weak 'warning' (prepulse) stimulus. PPI has been found to be disrupted by various drugs affecting the serotonin system, and is deficient in patients with schizophrenia and those with schizotypal personality disorder (Cadenhead et al., 1993). As MDMA stimulates the release of 5-HT, it was hypothesised that humans would exhibit the same reduction in PPI as rats do after MDMA administration. However, the results showed that a dose of MDMA sufficient to induce the expected psychological effects (1.7 mg/kg) *increased* PPI in humans, indicating a greater suppression of startle response after the prestimulus. The authors are unsure if these surprising results were a result of procedural differences, "a species-specific difference in the mechanism of action of MDMA, or a different behavioural expression of a similar pharmacological effect" (Vollenweider et al., 1999).

Studies of the physiological effects of MDMA have shown that it causes an increase in blood pressure and heart rate (de la Torre et al., 2000b; Freedman et al., 2005; Grob et al., 1996; Lester et al., 2000; Liechti & Vollenweider, 2000; Mas et al., 1999; Tancer & Johanson, 2003) and some have shown a slight increase in temperature (Freedman et al., 2005; Liechti & Vollenweider, 2000). Gamma et al. (2000) examined changes in regional cerebral blood flow alongside psychological changes in healthy volunteers administered MDMA. They found decreases in limbic, paralimbic, central, frontal and temporal areas, and increases in the inferior temporal and cerebellar cortex. Harris et al. (2002) found that 1.5mg/kg MDMA caused significant increases in plasma cortisol and prolactin 2-2.5 hours after administration, although some of the participants had high levels of recreational drug use which may have affected the results. Mas et al. (1999) administered a 75mg and a 125mg dose of MDMA to male participants and found increased plasma cortisol after both doses, but increased prolactin only after the high dose. Similar results were found by de la Torre et al. (2000b): increases in cortisol were found following 75mg, 100mg and 125 mg of MDMA, whereas prolactin increased significantly only after doses of 100 & 125mg in male volunteers. Pacifici et al. (2001) also found significant increases in cortisol 2hrs post administration of 100mg of MDMA. Forsling et al. (2001) administered a low dose of MDMA (40mg) to 8 male volunteers and found an increase in vasopressin (anti-diuretic hormone). They concluded that this was unlikely to be a result of a generalised stress response as it was not accompanied by an increase in cortisol. This finding has important implications for MDMA users as it indicates the importance of monitoring excessive fluid intake due to the increase risk of hyponatraemia. An interesting finding of this study was a negative correlation between vasopressin and plasma levels of MDMA: the authors suggest that this could indicate that the pharmacological response to MDMA is mediated by its metabolites.

MDMA has also been found to reduce immune system functioning following a 100mg dose (Pacifici et al., 2001). Evidence of this is seen as soon as 1 hour after administration and is increased when MDMA is combined with ethanol (0.8g/kg). Although it returns to baseline after 24 hour this clearly has implications for the health of recreational users. Hernandez-Lopez et al. (2002) found than administration of 0.8g/kg of ethanol with 100mg of MDMA caused higher plasma

concentrations of MDMA that 100mg of MDMA alone, whereas plasma concentrations of alcohol decreased when administered in combination with MDMA. To investigate the role of different neurotransmitters and receptors in mediating the effects of MDMA, several studies have been carried out in which a drug has been administered prior to MDMA as a pretreatment. Liechti et al. (2000a) argued that animal studies indicate that MDMA's effects are due to its interaction with the 5-HT transporter. To test this theory they administered 40mg of citalopram, an SSRI, before a 1.5mg/kg dose of MDMA. The results showed that citalopram pretreatment decreased most of the psychoactive effects of MDMA including increases in positive mood, feelings of depersonalization and derealisation and thought disorder. The cardiovascular effects were also attenuated by citalopram pre-treatment (Liechti & Vollenweider, 2000). These results support the hypothesis that MDMA causes its effects through interaction with 5-HT transporters. Liechti et al. (2000b) also found that pretreatment with the 5-HT_2 antagonist kentanserin attenuated the perceptual effects of MDMA, while feelings of heightened mood were unaffected. This indicates that stimulation of the 5-HT_2 receptor is responsible for the mild hallucinogen-like effects of MDMA. This is in accordance with evidence that correlates the hallucinogenic effects of LSD with 5-HT_2 receptor activity. Liechti & Vollenweider (2000) administered 1.4mg of haloperidol, a dopaminergic D_2 antagonist, intravenously to 14 subjects prior to administration of 1.5mg/kg of MDMA. This pretreatment reduced the euphoric effects of MDMA, indicating that dopamine release may contribute to the elevation of mood caused by the stimulant-type action of MDMA.

1.7.2 Acute effects of MDMA on cognitive function

Very few studies of the acute effects of MDMA have examined cognitive function. In an early uncontrolled study, Downing (1986) assessed short-term memory function using a digit repetition task and a short maths test. He found that after ingestion 0.8-1.9mg/lb of MDMA there was no change from baseline in digit repetition.

He did, however, find that participants had difficulty with the multiplication problems, apparently due to difficulty concentrating on the task. He also found that their judgement was impaired, demonstrated by the idiosyncratic responses to hypothetical problems requiring decision making. However, Downing's (1986) study was not controlled; it had no placebo condition, the majority of participants used MDMA twice monthly, 56% regularly used cannabis and two had severe eye conditions. Furthermore, the amount of MDMA taken varied across participants making it difficult to accurately interpret the results.

Vollenweider et al. (1998) conducted a double-blind placebo controlled cross-over study. He administered the Stroop test to healthy volunteers after 1.7 mg/kg of MDMA and found no difference in reaction time or error compared to the placebo condition. It was argued, however, that this was due to the short time span during which attention was required. It is also possible that the identification of colour necessary for this task was made easier by the heightened sensory perceptions often reported in acute studies of MDMA. Cami et al. (2000) found no differences on various tests of reaction time after administration of 75mg and 125mg of MDMA or placebo to 8 healthy participants (Vienna Reaction Unit – measure of sensory motor performance). They did, however, find that the higher dose of MDMA (125mg) caused a decrease in number of correct responses in the Digit Symbol Substitution Test (DSST - part of the Weschler Adult Intelligence Scale that evaluates the recognition and recoding of visual information). This difference was only evident during the peak effects of the drug. De la Torre et al. (2000b) administered the same battery of tests to 27 volunteers after administering various doses of MDMA ranging from 50 – 150mg. Although participants reported feelings of confusion, mental slowing and impaired attention, MDMA caused only a slight, non-significant impairment on the DSST, which was due to increases in response time rather than increases in errors. A similar pattern of results was found on the DSST by Hernandez-Lopez et al. (2002) and Farre et al. (2004).

Lamers et al. (2003) administered a battery of tests designed to examine psychomotor skills, attention and executive function to 12 participants after administrating 75mg of MDMA. There was no evidence of impairment in executive function or semantic retrieval as measured by the Tower of London task

and a verbal fluency task. In addition, MDMA *improved* performance on tracking tasks, even under divided attention conditions. Only estimation of object movement was impaired by MDMA. Recently, Ramaekers & Kuypers, (2005) assessed the effect of 75mg and 100mg of MDMA on 3 measure of behavioural impulsivity. They administered a stop-signal task, a go/no go task and the Iowa gambling task to 18 participants. They found that MDMA decreased reaction times to stop signals and interpreted this as increased impulse control. However, as no effect of MDMA was found on any other task they concluded that MDMA improved motor impulsivity, or response inhibition, rather than cognitive impulsivity. On the other hand, 0.06g/dl alcohol increased commission errors in the stop-signal task and in the go/no go task indicating an impairment in response inhibition. There were no MDMA x alcohol interactions on any of the tasks. Kuypers & Ramaekers, (2005) administered 75mg MDMA, 20mg methylphenidate and a placebo to 18 participants in a 3-way cross-over design. Ninety minutes after drug administration they administered 3 tests of cognitive function: the Rey Auditory Verbal Learning Task (RAVLT; Rey, 1958), a syntactic reasoning task designed to assess working memory, and the DSST. The only significant effect found was an impairment in immediate and delayed word recall in the MDMA condition compared to placebo. Interestingly, a normal pattern of word learning was observed suggesting that MDMA may increase forgetting rather than impair learning. Clearly, more systematic research is required to obtain a more comprehensive view of the acute cognitive effects of MDMA in humans.

1.7.3 Summary

Controlled laboratory based investigations of the subjective effects of MDMA have shown increases in energy, euphoria and empathy. Heightened perception of sound and colour has also been reported. Empathic subjective effects such as feeling close to others seem to be unique to MDMA in comparison to other stimulants. The peak effects of MDMA are experienced 90-120 after ingestion and can last between 2-5 hours (see Table 1). Physiological changes following MDMA administration include increased heart rate and blood pressure, and some studies found an increase in body temperature. MDMA caused the release of cortisol, prolactin and

vasopressin. Plasma MDMA appears to increase in a non-linear fashion, with increased doses producing disproportionate increases in plasma MDMA. Of the few studies have assessed the acute effects of MDMA on cognitive function, most have found little evidence of impairments. In fact, MDMA appears to *improve* motor impulsivity and performance on some tasks of attention.

1.8 Human Literature – Investigations of Recreational Ecstasy Users

1.8.1 The sub-acute effects of ecstasy

Although few controlled studies of the effects of MDMA have investigated its effects beyond several hours after administration, some have found effects lasting several days beyond acute administration. Vollenweider et al. (1998) found that symptoms including suppressed appetite, thirst, restlessness, lack of energy and insomnia were present in almost half of their participants 24 hours after ingesting 1.7 mg/kg of MDMA. Liechti & Vollenweider (2000) found that lack of appetite, difficulty concentrating and lack of energy were still reported in a minority of participants up to 3 days after being administered 1.5mg/kg of MDMA. They also found that one third of their participants showed some sign of depressed mood within the three days following MDMA. However, similar results were also found following pre-treatment with citalopram, and with citalopram alone. Thus, the results could reflect recovery from drug administration in general rather than a specific effect of MDMA. Kuypers & Ramaekers (2005) assessed cognitive function and mood the day after administration of 75mg MDMA (see section 1.7.2). Acutely, MDMA impaired performance of a verbal word learning task, but in contrast no impairments were found on this or the other tasks administered 24 hours after MDMA administration. Although increased self-ratings of fatigue and decreased vigour were apparent in the MDMA condition on the second day of testing, there were no differences in depression (Hamilton Depression Rating Scale) or other mood factors (Profile of Mood States).

It is possible to administer one or two doses to human volunteers to observe the effects of the drug in a controlled environment, but when investigating the effects of

more frequent or heavy use of the drug, administration is no longer possible due to ethical and legal considerations. Instead, field-based studies with recreational users have to be undertaken. These studies are generally carried out in nightclubs or parties. They compare participants who report using ecstasy on that night and those who have not, on test sessions over several days. This approach, described in more detail below, lacks a great deal of the validity that comes with controlled laboratory based studies of the effects of MDMA. There are several methodological flaws that could generate confounding factors that influence any results obtained. There is no control or clear evidence of the amount of MDMA ingested on the night due to the large variation of quantity of MDMA found in illicit ecstasy tablets (e.g. 20-110mg; Cole et al., 2002a). It is often reported that other recreational drugs are also used on the night of the study, although often no precise information is provided about quantities. Issues that affect all retrospective investigations of drug users are discussed in detail in section 1.8. In the remainder of the present section I will discuss studies of sub-acute effects of MDMA in recreational users.

Several studies have attempted to assess the sub-acute effects of MDMA by testing participants when they report using ecstasy, for example at clubs and parties, and again several days later. Control participants, those who do not report using ecstasy, are tested at the same locations. Curran & Travill (1997) used this design to compare cognitive function and mood in those who had taken ecstasy with those who had drunk alcohol, on day1 (in the club), day 2 and day 5 after ingestion. On all days they found that immediate and delayed prose recall tended to be impaired in MDMA users, although this result failed to reach significance ($p<0.06$), and both groups improved over the days. They also carried out the Serial Sevens task, which taps concentration and working memory. On this task they found that the MDMA group made fewer subtractions on all the days, with the difference being most evident on day 2. Parrott & Lasky (1998) administered an auditory word recall test and a visual search task to participants tested when they were drug-free (to establish a base line), on the night of drug consumption, 2 and 7 days later. Although the results showed that ecstasy users scored significantly worse than controls on all test sessions for both tasks, the differences was most marked on the night of drug use. As the impairments are evident even at baseline the authors conclude that this is

evidence of impaired cognitive function in ecstasy users caused by MDMA neurotoxicity.

Many ecstasy users report experiencing the 'mid-week blues' after taking the drug at the weekend, feelings of low mood and lethargy that last for several days. Verheyden et al. (2003a) found that 83% of the 430 ecstasy users that completed a questionnaire survey reported experiencing poor moods midweek following ecstasy use. Topp et al. (1999) also reported problems such as irritability, energy loss and trouble sleeping during the period after ingesting ecstasy. These findings support findings from Curran & Travill's (1997) investigation, in which the self-ratings of ecstasy users indicated significantly elevated mood on day 1 (in the club), but significantly lower mood on day 5 compared to controls. At the mid-week test session some of the ecstasy users scored within the range for clinical depression as measured by the Beck Depression Inventory (BDI - Beck, 1978). As ecstasy users often report disturbed sleep and eating patterns, the BDI scores were reanalysed without the somatic items to establish whether the somatic effects of MDMA were contributing to the differences in depression scores. They found that the differences were still significant. These results are supported by Parrott & Lasky (1998) who found that MDMA users reported higher levels of depression, sadness, unsociability and unpleasantness compared to controls two days after taking ecstasy. They also found that after 7 days all participants had returned to base line. They suggest that this lowering of mood is due to temporary serotonergic depletion due to MDMA's inactivation of tryptophan hydroxylase. However, the measure used to assess mood was a series of visual analogue mood rating scales that have not been validated. It is possible that ecstasy users rate themselves in a different way from the non-users, especially given that the ecstasy users failed to rate themselves as significantly more euphoric on the night of drug use.

Verheyden et al. (2002) investigated the 'mid-week blues' by assessing depression and aggression in 40 regular ecstasy users who had taken the drug on the night with 40 controls who had little or no experience of MDMA and had not taken it on the night. There were 2 test sessions: the night of drug use (day 0) and 4 days later (day 4). Further, due to evidence of gender differences in depression and aggression, this was also investigated by comparing men and women. Once again

the results showed an increased in BDI scores in ecstasy users mid-week, and interestingly, the increase was significantly greater in females than in males. The ecstasy group also had higher self-rated aggression scores mid-week compared to controls (Aggression Rating Scale, ARS, Bond & Lader, 1986), although there were no gender differences evident on this variable. It is important to note, however, that the ecstasy users were, on average, two years older than the control group, and had higher usage of other drugs including cocaine, ketamine, LSD and alcohol. They also took more cannabis than the control group between the 2 test sessions. All these factors could have affected the results. There is also the possibility that there were pre-existing differences between the groups, although the authors dismiss this as there were no differences found in measures of trait depression, anxiety or aggression measured on day 4. Again, the problem of control over the quantity of MDMA taken on the night of the study is present, and although males and females reported taking a similar numbers of ecstasy tablets, the amount of MDMA in each tablet is known to vary enormously (see section 1.8.2). The question of whether MDMA had been taken at all was addressed by the fact that the bodily symptoms scales showed that the MDMA group experienced effects such as visual sensitivity, loss of appetite and muscular tension, symptoms that have been shown to be associated with MDMA use in controlled studies of MDMA administration. This was supported by the fact that the users' pulse rate was considerably higher on day 0 than day 4 (but this information was available for only half of the participants). Although it is possible that all of these effects could be caused by the use of stimulants other than MDMA, all participants believed they had taken ecstasy and the great majority of ecstasy tablets do contain some MDMA (for review see Parrott, 2004a). The authors maintained that the changes in mood could not be attributed to a contrast between the 'high' at the weekend and normal life mid-week because of the differences between male and female participants, which would not exist it this were the case. They also found that there were no correlations between mood and lifetime usage of MDMA, and as there were also no differences in trait depression, they concluded that the results suggest mood lowering due to temporary mid-week depletion of 5-HT rather than long-term neurotoxicity. Interestingly, although there were no gender differences in aggression mid-week, there was a correlation between number of tablets taken on day 0 and aggression scores for male participants only. This pattern was also seen

for female participants only for their depression scores. The authors suggested a more sensitive measure than a self-rating scale is needed to pick up differences in aggression between male and female MDMA users.

In an attempt to avoid the problems associated with demand characteristics of self-rating scales, Curran et al. (2004) found increased aggression in ecstasy users compared to controls mid-week using a more objective task tapping cognitive bias toward material with an aggressive content (see Chapter 6). However, as the task was only administered on the mid-week test session it is possible that the ecstasy users were more aggressive than controls over all rather than it being a transient, mid-week phenomenon. The study did, however, support the idea than the increased depression found mid-week in ecstasy users is transient: although self-rated depression scores were significantly higher in ecstasy users than controls at the mid-week test session, this difference was no longer present a week after acute ecstasy use.

1.8.2 Methodological problems

Most studies investigating the effects of chronic ecstasy use in humans use cross-sectional designs to compare groups of recreational ecstasy users with control participants who have never taken the drug. Controlled investigations of the use of MDMA at doses that are suspected to be neurotoxic cannot be carried out due to ethical considerations. Thus, the existence of methodological problems inherent in this type of design cast doubt on the validity of the conclusions drawn from the data obtained. As with any retrospective study, there is always a possibility that any observed group differences reflect pre-morbid differences between the groups. For example, several studies have reported increased impulsiveness in MDMA users (e.g. Parrott et al., 2000), even when compared to matched controls who used cannabis (Tuchtenhagen et al., 2000). However, it could be argued that this difference would be expected at baseline in a population that are inclined to regularly take illicit drugs, and this would be more pronounced in those taking class A drugs that those who occasionally smoke cannabis. MDMA is thought to be neurotoxic to the serotonergic system, but as many of the mood alterations

attributed to MDMA use are also linked to 5-HT function, pulling apart the pre-existing traits and the consequences of MDMA use is impossible using a cross-sectional design. Pre-existing psychiatric problems may predispose people to self-medicate with ecstasy. For example, depressed or socially anxious people may take the drug to temporarily feel close to others.

The sampling methods used by researchers into could also affect the outcome of studies. The 'snowball technique' (Solowij et al., 1992) is widely used: participants who hear about the research recruit from among their peers. Often, this occurs within a higher education setting, leading to the sampling population commonly being small and unrepresentative. Only 13% of university students report having taken ecstasy (Webb et al., 1996). The fact that the sample is also self-selected is problematic due to the possibility that participants who volunteer for research have pre-existing fears and beliefs about the effects that MDMA may have had on them.

Another major problem facing studies of recreational ecstasy users is the issue of finding an appropriately matched control group. It is not only necessary to match participants for age, gender, premorbid intelligence etc., but on other factors like prior use of other illicit drugs. This is of particular relevance as the majority of recreational ecstasy users use a range of other drugs (including cannabis, cocaine, amphetamines and LSD), and the use of these drugs tends to increase in parallel with ecstasy use (Parrott et al., 2001). Thus, recruiting subjects who have never taken ecstasy and yet have used as many other drugs as those who do use it is very challenging. The vast majority of ecstasy users smoke cannabis, some habitually and some simply to alleviate the negative symptoms associated with 'coming down' from the euphoric high of MDMA. As cannabis has been found to cause memory deficits in humans and has been implicated as being a contributing factor to a variety of psychopathologies such as paranoia and psychosis (Semple et al., 2005), it is essential to match for its use across groups. The main action of LSD is on the serotonin system, and the use of this drug is often not controlled for in studies comparing controls with ecstasy users.

A related issue concerns aspects of the life style associated with ecstasy use. As the majority of ecstasy users take the drug at clubs and raves, it is important that the

control group also comes from within this social subgroup to ensure that observed differences are not caused by lifestyle differences. Clubbing often involves physical exertion for prolonged periods and very late nights, which are likely to alter sleep patterns. Cole et al. (2002b) cite the example of airline stewardesses, who experience similar shifts in circadian patterns and also show alterations in cognitive function (Cho et al., 2000). Recently, attempts have been made to overcome the problem of disturbed sleep patterns in ecstasy users by ensuring that all participants have at least seven nights of 7-9 hours of continuous sleep prior to testing (Zakzanis et al., 2002; Zakzanis & Young, 2001b).

An issue that has yet to be resolved is the abstinence period required to ensure that any results found are tapping into the long-term effects of MDMA rather than the acute or residual effects of the drug. Most studies have used a 2-3 week abstinence period which may not be long enough to make inferences about long-term effects, especially as research with rats suggests 3 weeks is needed for TPH activity to return to normal after MDMA (Rattray, 1991). That ecstasy use has acute and residual effects does not imply permanent neurotoxic damage. The reliability of self-reported abstinence is also questionable. While most studies simply accept participants self-reported abstinence lengths, others use blood and urine screening to verify, but as MDMA is only detectable in blood and urine for 24-48 hours, this provides limited information. A more accurate, and considerably more expensive, method is hair analysis, where one centimetre of hair can provide the drug use history over the past month.

A methodological issue associated with the majority of studies of ecstasy users is the lack of control over, or knowledge about, the precise amount of the drug consumed. This is partly due to the use of self-reported drug use histories. As ecstasy is mostly used concurrently with other drugs that are known to affect episodic memory (e.g. cannabis and alcohol), it is likely that the participants' memory of drug taking incidents is poor. Cooper et al. (2000) carried out a study of 100 drug users from within the dance scene and found a concordance rate of only 50% between self reported drug use and forensic hair analysis. Even if the ecstasy users' memory of the drug taking episode is not impaired, the actual quantity of MDMA consumed can only be roughly estimated. Saunders (1995) found that

tablets sold as ecstasy often contain derivatives of MDMA, such as MDA (3,4-methelenedioxy-amhetamine) or MDEA (3,4-methelenedioxy-ethylamphetamine). In a recent review Parrott (2004a) concludes that the majority of ecstasy tablets contain MDMA, although in the mid-90s 4-20% contained other drugs such as caffeine, amphetamine, ketamine and ephedrine. The dose of MDMA in each tablet varies a great deal, with one study finding concentrations ranging from 20-109mg (Cole et al., 2002a). Thus, precise knowledge of dosage is impossible, even if self-reported drug use histories are 100% accurate. Additionally, some studies (e.g. McCann et al., 1999b) do not provide a complete drug use history. Instead, they simply ask participants whether or not they have taken a drug at least once. This can be misleading, as groups can appear to have no significant differences in prior drug use, whereas in reality a participant who has taken a drug once has been categorised the same as a participant who has taken the drug regularly for several years.

1.8.3 Neurobiological investigations of serotonergic function in ecstasy users

1.8.3(i) Cerebrospinal Fluid Studies (Table 2)

The existence of serotonergic neurotoxicity following MDMA use is, of course, far more difficult to establish in humans than in animals. A range of indirect measures have been used to assess 5-HT function. One such method is to investigate the concentration of 5-HIAA in cerebrospinal fluid. 5-HIAA is a metabolite of serotonin, thought to serve as a marker of central serotonin function. Although the first experiment using this technique failed to demonstrate any differences between the groups (Peroutka et al., 1987), since then four studies from the same laboratory have reported that recreational ecstasy users have lower concentrations of CSF 5-HIAA than participants who have never used ecstasy (Bolla et al., 1998b; McCann et al., 1999b; McCann et al., 1994; Ricaurte et al., 1990). Bolla et al. (1998b) found a negative association between monthly dosage of ecstasy and CSF 5-HIAA ($r = -0.519$, $p < 0.03$). However, it is necessary to take into account that CSF levels of 5-HIAA are naturally extremely variable, and are affected by many things such as season, diet, activity and menstrual cycle which were not controlled for in these studies. In addition, although 5-HIAA is a metabolite of 5-HT and a reduction in its

concentration would indicate lower levels of 5-HT in the brain, this is not necessarily evidence of neurotoxic damage to the serotonergic system. As MDMA has been shown to inactivate tryptophan hydroxylase (TPH), low levels of serotonin would be expected until TPH activity returned to normal and this could take over 2 weeks after acute MDMA administration (Rattray, 1991). After chronic use recovery could take longer, and many of the participants in these studies had abstained from taking ecstasy for only 2 weeks. Low levels of CSF 5HIAA have could also be due to pre-existing differences in the serotonergic system. For example, alterations in 5-HIAA have been associated with impulsive personalities (see section 1.5.3). However, it should be noted that the differences in CSF 5-HIAA are consistent with animal studies investigating the effects of MDMA administration, which show similar alterations in non-human primates after neurotoxic exposure (Insel et al., 1989; Ricaurte et al., 1988a).

1.8.3(ii) Neuroendocrine challenges

An alternative approach to indirectly measuring serotonergic function in humans is to administer a neruoendocrine challenge, in which levels of serotonin in the brain are manipulated, and to measure the hormonal responses to these manipulations. L-tryptophan increases prolactin, and this prolactin response is thought to provide a measure of central 5-HT function in humans. Two early studies administering L-tryptophan challenges to ecstasy users found conflicting results. In both studies participants were administered 7g of L-tryptophan diluted in saline solution infused over 20 minutes. Blood was taken regularly for 2 hours after administration to measure prolactin. Peak change in prolactin was calculated by subtracting the baseline value from the highest level found. Price et al. (1989) found that nine ecstasy using participants showed a less pronounced prolactin increase following L-tryptophan compared to an equally small number of controls, and the authors attributed this blunted response to altered serotonergic function caused by MDMA neurotoxicity. McCann et al. (1994) found no differences in response to L-tryptophan between ecstasy users and controls. They suggest that their lack of positive findings could be attributed to the long abstinence period in their participants (average of 18 weeks). However, some participants were only abstinent for 2 weeks, and as the participants in the Price et al. (1989) study were abstinent for at least 20 days it is unlikely that this caused the disparity in the

results. In addition, while the control participants had been recruited locally, the ecstasy users tested in Price et al.'s (1989) study had been flown in the previous day to participate in the study, a factor that may have affected their prolactin response. It is also worth noting that there was in fact no significant difference in peak change between the two groups. Price et al.'s (1989) interpretation of blunted prolactin response to L-tryptophan arises from the fact that the ecstasy users' increase in prolactin was a trend, whereas it was significant in the non-user group.

Evidence suggesting that blunted prolactin and cortisol response following fenfluramine administration are associated with impairments of the serotonergic system (Newman et al., 1998) have lead to researchers using the drug as a tool to investigate serotonergic function in ecstasy users. Gerra et al. (2000b) investigated prolactin and cortisol response to d-fenfluramine in ecstasy users who had been abstinent for 3 weeks compared to controls, and then followed up all participants after 12 months of abstinence. Results indicated that ecstasy users showed significantly lower increases in plasma prolactin and cortisol 3 weeks after discontinuation of ecstasy use. Although prolactin response was still blunted after 12 months, cortisol responses appeared to be restored. However, all ecstasy using participants involved in this study were taking part in a 12 month drug rehabilitation programme by choice, and thus were not well matched to the control group who were recruited from hospital staff and students who had never used psychoactive drugs. The ecstasy users had a history of use of other drugs, and although urine tests were carried out 3 times a week to ensure ecstasy was not used, use of cannabis, alcohol and even opiates did not lead to exclusion from the study. The ecstasy users showed increases in novelty-seeking behaviours at both time points, and prolactin response was negatively correlated with this scale. This is particularly important as prolactin responses to d-fenfluramine have been shown to be strongly inversely correlated with impulsivity in male offenders (Dolan et al., 2001), indicating that the differences in responses to d-fenfluramine between the ecstasy and control groups could precede the onset of ecstasy use.

Once again, the difference in levels of poly-drug use in ecstasy users compared to controls is of great importance when investigating responses to neuroendocrine challenges. Prolactin response to d-fenfluramine has been found to be blunted in

both post-withdrawal alcoholics (Farren et al., 1995) and those simply defined as heavy drinkers (Balldin et al., 1994). This pattern of reduced response to d-fenfluramine was also found in abstinent heroin addicts, where once again it was found to be negatively correlated with novelty seeking scores (which were much higher in the heroin addicts than in the control group) (Gerra et al., 2000a). Blunted prolactin response has also been found in hospitalised cocaine addicts (Buydens-Branchey et al., 1999). Verkes et al. (2001) attempted to overcome the confound caused by the use of other drugs by excluding participants with current use of cocaine, amphetamines and opiates, and the use of more than 3 units of alcohol per day. Both heavy (over 48 occasions) and moderate (12-48 occasions) ecstasy users were found to have reduced release of cortisol after d-fenfluramine compared to controls. Although there was a trend toward lower increases in prolactin in the ecstasy users, it failed to reach significance. The authors claim that this is due to the large amount of variability in responses, and also point out that Gerra et al. (2000b) found a similar pattern of more pronounced effects of d-fenfluramine on cortisol than prolactin on the first test session 3 weeks after cessation of ecstasy use (although in this case both were significantly blunted). However, as some of the ecstasy users had used ecstasy only two days before the study it is possible that the responses to d-fenfluramine are more representative of the sub-acute or residual of MDMA, rather than reflecting long-term neurotoxic effects of the drug. Although attempts were made to control for the use of other drugs, the ecstasy users showed much higher levels of cannabis use. Gouzouliz-Mayfrank et al. (2002) attempted to separate out the effects of MDMA and cannabis using a fenfluramine challenge. They compared ecstasy users who also used cannabis with a control group that exclusively used cannabis and a non-drug using control group. Although previous cannabis use was similar in the two drug using groups, the ecstasy users had used it for longer. Regular users of other drugs were also excluded (regular use was defined as once a month for six months or longer within the last 2 years), as were those who reported heavy alcohol use (drunkenness at least twice a month). However, due to the withdrawal of d-fenfluramine from the market before completion of the experiment, the authors could not compare all the groups. They compared female ecstasy users with non-drug using females. They found a trend towards lower peak prolactin response in ecstasy users, but no statistically significant difference. More interestingly, they were also able to compare males

who exclusively used cannabis with males who used both ecstasy and cannabis. They found that the male cannabis only users showed a significantly lower peak prolactin response than those who used both ecstasy and cannabis. Although it was not possible to compare these groups with a non-drug using control, it was noted that both user groups showed blunted prolactin responses compared to control groups reported in previous literature. The most important finding, however, was that consistent associations were found between neuroendocrine response and previous cannabis use, whereas associations with previous ecstasy use were "weak and inconsistent". Although this study was limited due to the fact that it could not be completed, it indicates the importance of controlling for cannabis use. It also highlights the possibility that cannabis use could be an important confound in previous studies using neuroendocrine challenges to investigate changes in serotonergic function in ecstasy users.

M-chlorophenylpiperazine (m-CPP) is a serotonin releaser and postsynaptic receptor agonist that has been regularly used as a neuroendocrine probe to investigate serotonergic function in psychiatric patients. It increases plasma cortisol and prolactin, and has been shown to increase anxiety in healthy volunteers. In patient groups, m-CPP causes syndrome–specific relapse of symptoms. McCann et al. (1999a) measured the neuroendocrine and behavioural response to 0.08 mg/kg m-CPP administered intravenously as a 90-second infusion. Although they compared 25 ecstasy users and 25 controls, all of whom had been abstinent from all psychoactive drugs for 3 weeks, neuroendocrine information was only collected for male participants (17 in each group). M-CPP-induced increases in plasma cortisol and prolactin were lower in the male ecstasy users than in the male controls, although only cortisol showed a significant difference between the groups when comparing peak difference from baseline levels. Subjective effects were assessed in both male and female users. Overall, ecstasy users reported more positive mood responses, and less negative symptoms than controls. In fact, 8 of the control group had panic attacks compared to only one ecstasy user. The authors suggest that the subjective differences could be due to blunted neuroendocrine activity, or that it could be a result of ecstasy users being more used to altered states of consciousness, and viewing them as more favourable.

Table 1.2: Investigations of 5-HT function comparing ecstasy users and controls

Method / author	Technique	Marker	Evidence of group differences?		Correlation with ecstasy use?
SPECT			**Current**	**Ex-users**	
Semple et al. (1999)	[^{123}I]β-CIT	SERT	√	*	√ **time since last use only**
Reneman et al. (2000a)	[^{123}]I-5-I-R91150	5-HT_{2A} receptors	√	*	**X**
Reneman et al. (2001b)	[^{123}I]β-CIT	SERT	√	**X**	**X**
Reneman et al. (2001a)	[^{123}I]β-CIT	SERT	√ **heavy female users only**	**X**	√ **females only**
PET					
McCann et al. (1998)	[^{11}C]McN5652	SERT	√	*	√
Obrocki et al. (1999)	FDG	Cerebral glucose metabolic rate	√	**X**	**X**
Buchert et al. (2001)	FDG	Cerebral glucose metabolic rate	√	**X**	√ time since last use only
Gamma et al. (2001)	$H_2{}^{15}O$ + vigilance task	Regional cerebral blood flow	**X**	*	**X**
Buchert et al. (2003)	[^{11}C](+)McN5652	SERT	√	**X**	*
Thomasius et al. (2003)	[^{11}C](+)McN5652	SERT	√	**X**	**X**
Buchert et al. (2004)	[^{11}C](+)McN5652	SERT	√	**X**	√ time since last use & dose
McCann et al.(2005)	[^{11}C](+)McN5652 [^{11}C]DASB	SERT SERT	√	**X**	√ time since last use & dose
Neuroendocrine challenge					
Gerra et al. (1998)	D-fenfluramine	PRL & CORT response	√	*	**X**
Gerra et al. (2000b)	D-fenfluramine	PRL & CORT response	√	√ CORT only	√ length of use
Verkes et al. (2001)	D-fenfluramine	PRL & CORT response	√ CORT only	*	*
Price et al. (1989) (T+)	Tryptophan	PRL & CORT response	√	*	**X**
McCann et al. (1994) (T+)	Tryptophan	PRL response	**X**	*	**X**
Curran & Verheyden (2003)(T+ & T-)	Tryptophan	Plasma TRP & behavioural	**X**	√ T+ only	**X**
McCann et al. (1999a)	M-chlorophenylpiperazine	PRL & CORT response	√ PRL only	*	**X**
Monoamine metabolites					
McCann et al. (1994)	Cerebrospinal fluid tap	5-HIAA	√	*	**X**
McCann et al. (1999b)	Cerebrospinal fluid tap	5-HIAA	√	*	*
Bolla et al. (1998b)	Cerebrospinal fluid tap	5-HIAA	√	*	√ dose only
Plasma concentrations					
Stuerenburg et al. (2002)	Blood samples	5-HIAA & 5-HT	**X**	**X**	**X**

* not tested / reported ; √ differences found; **X** no differences found

FDG –2-[(^{18})F]-fluoro-2-deoxy-D-glucose; **BOLD** - blood oxygenation level-dependant: **PRL & CORT** – prolactin & cortisol

They also argue that the difference in neuroendocrine response to m-CPP could reflect MDMA-induced alterations in 5-HT function. However, they do concede that animals who have undergone lesioning with 5-HT neurotoxins show *increased* neuroendocrine responses to m-CPP, rather than the blunted responses seen in ecstasy users in the present study. The authors claim that this is not an entirely contradictory finding as the ecstasy users have been using the drug for an average of 5 years, and thus there is a possibility that compensatory neural mechanisms have developed over that time. They also quote the example of healthy volunteers being found to have blunted neuroendocrine response to m-CPP following tryptophan depletion, claiming it is consistent with their own findings. However, the fact that the results of the present study more resemble those found after tryptophan depletion indicate that they could be reflecting a temporary depletion of brain 5-HT, rather than persistent MDMA-induced 5-HT neurotoxicity, as suggested by the authors.

1.8.3(iii) Neuroimaging Studies

A variety of neuroimaging techniques have also been used to investigate the effects of ecstasy. Chapter 3 provides an in depth discussion of the research investigating serotonin transporter density in recreational ecstasy users and this will not be covered again here.

In a series of studies Reneman et al. (2000a; 2000b; 2002b) used [^{123}I]R91150 labelled positron emission tomography (PET) to investigate 5-HT_{2A} receptors in ecstasy users compared to drug-naïve controls. They found that while ecstasy users abstinent for a week showed decreased binding to 5-HT_{2A} receptors compared to controls, ecstasy users abstinent for at least 2 months showed *higher* binding. In a parallel investigation in rats (Reneman et al., 2002b) they found a similar pattern of results: reduced density of 5-HT_{2A} receptors was evident both 6 hours and 3 days after MDMA administration, whereas 30 days after there was increased density. The authors concluded that these results reflect a down regulation of receptors in the sub-acute phase following MDMA-induced increase of synaptic 5-HT, and that they also provide a model of chronic use reflecting upregulation of receptors due to low levels of synaptic 5-HT. However, the numbers of participants in these studies were small, and although urine screens were used, these can only verify short term

abstinence for most drugs (24-48 hours). No information was provided about the use of other recreational drugs, and the control groups were drug naïve, increasing the likelihood that pre-morbid differences between the groups existed.

Gamma et al. (2001) used PET to investigate differences in brain activity (as shown by regional cerebral blood flow - rCBF) between regular ecstasy users and controls. Their rationale was that depressed patients, who are likely to have some disturbance to the serotonergic system, show alterations in cerebral blood flow. They found no differences in brain activity between the two groups. The fact that the control group were slightly older than the ecstasy using participants could influence the results due to evidence that rCBF decreases with age, but as the age difference is relatively small (3.4 years), the authors claim it is unlikely to be a major confound. These results are supported by Chang et al. (2000) who found no differences in rCBF between 21 ecstasy users abstinent for 2 weeks and age-matched drug-naïve controls.

Buchert et al. (2001) used PET with the 2-[18F]-fluoro-2-deoxy-d-glucose (FDG) ligand to assess glucose metabolism in the brains of 93 ecstasy users and 27 controls. They argued that changes in glucose metabolism could be a secondary effect of MDMA-induced damage to the serotonergic system. FDG uptake was reduced in the putamen, caudate and left amygdala of ecstasy users compared to controls. In addition, a correlation was found between time since last use and FDG uptake, with shorter abstinence times being associated with greater reductions of uptake. However, not only did this study employ far fewer controls than ecstasy users, but the control participants were all oncology patients, and the PET methodology differed between the groups. All of these factors may have affected the results.

1.8.4 Summary of the neurobiological studies of the long-term effects of ecstasy use

As pre-clinical studies have found evidence of serotonergic neurotoxicity, methods including PET, SPECT and neuroendocrine challenges have been used to

investigate serotonergic function in human MDMA users (see Table 2). Many have found evidence of alterations in the serotonergic system in current users, such as reduced binding to serotonin transporters and blunted responses to pharmacological challenges. Evidence has also been found, however, for recovery: ex-users have been found to have similar binding to controls in both PET (Thomasius et al., 2003) and SPECT (Reneman et al., 2001b) studies, and there is tentative evidence of recovery of hormonal responses to fenfluramine challenge (Gerra et al., 2000b). Interestingly, (Reneman et al., 2001b) found that although ex-users did not show reduced binding to serotonin transporters while current users did, both groups performed worse than controls on immediate and delayed recall. Thus, it appears that MDMA use does affect serotonergic function, but that these alterations may be reversible and independent from cognitive deficits.

The major problem with assessing serotonegic function in MDMA users compared to controls is that there may be some pre-existing differences in the serotonin system and these may make certain people more likely to use the drug. For example, 5-HT function has been associated with sensation seeking personalities, and with impulsive behaviours. These types of personalities could be more likely to experiment with recreational drugs. Levels of harm avoidance have been found to correlate with hormonal response to fenfluramine in healthy volunteers (Gerra et al., 2000c), thus individuals with altered 5-HT function could exhibit less harm avoidance and therefore be more likely to take part in possibly harmful activities like using recreational drugs.

1.8.5 Long-term effects of ecstasy use on memory and learning (Table 1.3)

As previously discussed, the results of studies reporting the neurotoxic effects of MDMA administration in animals have led to the hypothesis that MDMA could be neurotoxic in humans, with particular emphasis on its effects on the serotonergic system. Serotonin has been implicated in the regulation of many diverse human functions including cognitive function, although evidence for this association is mixed (see section 1.5.4). As exploring neurotoxicity in humans is complicated, and has yielded mixed results, many researchers have focused on investigating

possible functional consequences of this suspected neurotoxicity despite the absence of functional consequences in animals.

Several early case studies reporting memory problems in people who had used ecstasy (e.g. McCann & Ricaurte, 1991; Spatt et al., 1997) caused concern about the long-term effects of the drug. However, the majority of case studies are of patients who present with severe problems, and usually have a history of serious drug misuse or psychiatric illness. Although they can be interesting examples of possible acute reactions to ecstasy, they do not tell us about the majority of ecstasy users, those who use the drug recreationally once or twice a month and seem to do so with no apparent functional consequences on their day to day lives. Thus, the following section will focus on larger group studies of recreational ecstasy users.

All cross-sectional studies of ecstasy users are prone to the same methodological problems (see section 1.8.2), and earlier studies had yet to attempt to address these. Krystal et al. (1992) carried out the first group based study of ecstasy users. Although they reported deficits in the Wechsler Memory Scale delayed paragraphs test and on immediate and delayed figural recall, the scores of the 9 ecstasy users were compared to age matched norms rather than a real control group. It was also found that some of the participants had histories of psychiatric complaints, and the fact that they were administered a tryptophan challenge several hours before testing is likely to have confounded the results. Bolla et al. (1998b) compared 24 abstinent ecstasy users and 24 control subjects on several tests of memory and measured CSF-5HIAA (see section 1.8.3(i)). They reported that ecstasy users showed a significant impairment in immediate verbal and delayed visual memory. However, it is important to note here that the reported results only became apparent after the monthly dose of ecstasy was included in the regression analysis, prior to this no differences between the groups was evident. In addition, memory deficits were not associated with any other measure of exposure, for example life time usage, which could be expected to be a better indicator of chronic use, and thus of possible neurotoxicity. The results could also be questioned due to the numerous memory tests being condensed into the four categories presented: immediate and delayed visual memory, and immediate and delayed verbal memory. No theoretical explanation is given for this reduction, and there is no discussion of the increased

likelihood of type I on errors when using such a large number of sub-tests. Another apparent problem with this study is that although Bolla et al. (1998b) attempted to match the groups on prior drug use, they only asked participants if they had previously tried a drug, and no information is provided on the frequency of use. Even so, the results show that five times as many participants in the ecstasy group had used amphetamine and cocaine than in the control group, and that over three times as many had used LSD. Studies which fail to match participants in this respect run the risk of being interpreted as showing the cognitive effects of recreational drugs in general rather than of MDMA itself.

Parrott et al. (1998) administered a battery of cognitive tests to 10 'regular' ecstasy users (who had taken the drug on more than 10 occasions), 10 novice users (taken the drug 1-9 times) and 10 controls who had never taken the drug. Immediate and delayed word list recall was significantly impaired compared to controls in both user groups. However, as drug use histories were not taken it is difficult to interpret these results in relation to ecstasy use alone. There also seems to have been little attempt to match the control group with the ecstasy users on aspects such as pre-morbid IQ or educational level, all factors which could confound the results. Morgan (1999) compared 25 ecstasy users who had taken at least 20 ecstasy tablets, 22 poly-drug users who had never used ecstasy and 19 controls (non-users). They were tested using the immediate and delayed prose recall, taken from the Rivermead Behavioural Memory Test (RBMT), a test of everyday memory. Morgan (1999) reported that the ecstasy group performed worse than the poly drug group on both immediate and delayed recall. However, it was noted that the abstinence period for the ecstasy users varied from less than a week to over 6 months. The data was reanalysed after dividing the groups into three categories: abstinence periods of less than one month, between one and six months and over six months. A significant improvement was found as time since last use increased. It is possible that the observed differences came from residual effects of the drug. These results could also be interpreted as evidence for recovery from deficits caused by MDMA use, and thus cast doubts on the hypothesis of long-term neural damage (see section 1.11). Other factors that may have influenced the results include the fact that the poly-drug users had higher scores on pre-morbid IQ (from the NART) than the ecstasy group, and that in the ecstasy group, unlike the poly-drug group, 8

reported occasional use of benzodiazepines, two used ketamine and two used barbiturates. Bhattachary & Powell (2001) attempted to investigate the development of cognitive deficits in ecstasy users by comparing novice, regular and abstinent users with a control group matched for age, gender, educational level and verbal IQ. Novice users were defined as having used the drug 1-5 times, never more frequently than once a month and at least once in the last 21 days. Regular users had used the drug at least five times and at least twice in the last 21 days. Abstinent users had been regular users in the past, but had not used the drug for at least 30 days. None of the participants in this latter group had been abstinent for more than 120 days. A battery of cognitive tests was administered, and no differences were found between the groups on verbal IQ, visuo-spatial memory (Rey-Osterreith test) or working memory (backwards digit span). Once again, immediate prose recall was impaired in all ecstasy groups compared to controls, and delayed prose recall was impaired in all but the novice ecstasy users. Lifetime consumption of ecstasy was strongly correlated with scores on both tests. A major problem with the study is that detailed lifetime histories of drugs used other than ecstasy were not obtained from the participants. Only drug use in the past 30 days was reported, and even within this time, the ecstasy groups used significantly more cannabis than the control group, who had used none. The authors counter this argument by showing that cannabis use in the last month was not correlated with scores on any of the tests. However, if lifetime cannabis use was taken into consideration, this may not have been the case. There was also evidence that score on immediate and delayed recall improved as time since last use increased, up to about 15 days. This could indicate that residual effects of the drug may be present in both the novice and regular user groups, especially as some of the participants had used ecstasy only two days before the study. This short abstinence period could also mean that participants were experiencing the 'mid-week blues' associated with the several days following ecstasy use (see section 1.8.1). Low mood could be a confounding factor in cognitive tests but, as no mood assessments were used, it is impossible to confirm or deny this. The abstinence period for any recreational drug, including ecstasy, was only 24 hours, and as information was only provided about ecstasy it is impossible to know if the residual effects of other drugs such as alcohol and cannabis could influence the results.

Task		**Authors**	**√ – ecstasy users impaired O - No group differences**
Immediate recall	Prose	Morgan (1999)	√
		Rodgers (2000)	√ vs controls O vs cannabis users
		Bhattachary & Powell (2001)	√
		Fox et al. (2001a)	O
		Morgan et al. (2002b)	√
		Thomasius et al. (2003)	√ (ex-users only)
		Curran & Verheyden (2003)	√
		Hanson & Luciana (2004)	√
		Dafters et al. (2004)	O
	Word list	(Parrott & Lasky (1998)	√
		Reneman et al. (2000a)	O
		Gouzouliz-Mayfrank et al. (2000)	√
		Croft et al. (2001)	O
		Fox et al. (2001b)	√
		Simon & Mattick (2002)	O
		Curran & Verheyden (2003)	O
		Thomasius et al. (2003)	√ (ex-users only)
		Hanson & Luciana (2004)	√
		Dafters et al. (2004)	O
Delayed recall	Prose	Morgan (1999)	√
		Rodgers (2000)	√ vs controls O vs cannabis users
		Bhattachary & Powell (2001)	√ (not novice users)
		Fox et al. (2001a)	O
		Morgan et al. (2002b)	√
		Thomasius et al. (2003)	√ (ex-users only)
		Curran & Verheyden (2003)	O
		Hanson & Luciana (2004)	√
		Dafters et al. (2004)	O
	Word list	Parrott & Lasky (1998)	√ (ex-users only)
		McCann et al. (1999b)	√
		Reneman et al. (2000a)	√
		Croft et al. (2001)	O
		Gouzouliz-Mayfrank et al. (2000)	O
		Fox et al. (2001b)	√
		Simon & Mattick (2002)	O
		Curran & Verheyden (2003)	√ (ex-users only)
		Thomasius et al. (2003)	√ (ex-users only)
		McCardle et al. (2004)	√

Table 1.3: Comparisons of ecstasy users and controls on tasks tapping verbal learning and memory

Time since last use does not appear to be a predicting factor in the abstinent user group, although this group in general had a higher lifetime consumption of ecstasy than the other two user groups. Thus, the authors maintain that the results could reflect acute effects of ecstasy that subside over several weeks, and a more persistent detriment resulting from high cumulative lifetime use.

As previous literature appears to be indicating lasting impairments caused by ecstasy use, Zakzanis & Young (2001b) carried out one of the few longitudinal studies in ecstasy research, arguing that it was necessary to investigate possible progressive memory impairment. They studied the functional consequences of continued ecstasy use over a period of one year. They compared the results of memory tests of 15 ecstasy users on two test sessions 1 year apart. The participants abstained from all drugs for 2 weeks before each test session, and as ecstasy has been implicated in disturbed sleep patterns, the subjects were required to have had at least 7 nights of 7-9 hours sleep in order to ensure the effects of sleep deprivation did not confound the results. The Wechsler Adult Intelligence Scale III and the RBMT were administered at each session. Although the total score for the RBMT was found to have decreased over the one year period, further analysis revealed that only one sub-set had declined: immediate and delayed memory for a short passage of prose. No other changes were detected. They did, however, identify some correlations between various memory tests and duration and frequency of ecstasy use. Caution must be exercised in attributing declines in memory to MDMA as all the participants also used many other types of recreational drugs, and no control group was used in this study.

Thomasius et al. (2003) designed a study with the aim of attempting to separate out the effects of ecstasy from that of general poly-drug use, as well investigating recovery after ecstasy use. They compared four groups of participants; 30 current ecstasy users who reported using ecstasy an average of approximately 600 times (abstinent for 3 weeks); 31 ex-ecstasy users with a similar lifetime use of ecstasy who had not taken the drug for an average of approximately18 months; 29 poly-drug controls who had comparable lifetime use of other recreational drugs but no history of ecstasy use; and finally 30 drug-naïve controls. An attempt was made to

address some of the methodological problems apparent in previous studies by matching all groups for age, gender, level of education and both pre-morbid and current IQ. A comprehensive battery of cognitive tests assessing psychomotor speed, complex attention, executive function, learning and memory was administered to all participants. Positron emission tomography was also used to assess serotonin transporter availability (see section 3.1), and the SCL-90-R (Derogatis, 1994) to assess psychopathology (section 1.8.9).

Complex attentional skill (assessed by the Go/No go and divided attention sub-tests of a German attention test battery), psychomotor speed (trail making test A), executive function (trail making test B) and learning and memory (remembering phone numbers and company signs over a 30 minute period) showed no group differences. However, ex-users scored significantly worse than drug-naïve controls on both immediate and delayed prose recall, as well as on learning over trials and delayed recall on the auditory verbal learning test (AVLT). Poly-drug users scored significantly worse than drug-naïve controls on AVLT learning, as well as showing more preservative errors on the WCST, although this could be attributed to their higher cannabis consumption. It was noted that amount of cannabis smoked in the last year was the best predictor of AVLT, immediate and delayed prose recall scores.

The interesting picture to come out of this study is that current users appear to be cognitively unimpaired, while ex-users show deficits in learning and memory. The authors attempt to explain the cognitive deficit being apparently specific to the ex-users group by suggesting that memory deficits may appear after a certain period of abstinence. Alternatively, they suggest that the results may indicate a sampling problem. It is a possibility that the ex-user group may contain a disproportionate number of people who have experienced either cognitive or psychological problems that have prompted them to give up using ecstasy. This idea is countered, however, by qualitative data gathered that suggests that the majority of participants stopped using ecstasy for more general lifestyle reasons (i.e. 'matured out of the party scene'). Perhaps most importantly, no evidence was found to implicate ecstasy use *per se* with cognitive impairment, as no differences in performance were found between the two ecstasy using groups and the poly-drug control group.

1.8.6 Long-term effects of ecstasy use on executive functions (Tables 1.4 & 1.5)

Attempts to investigate the effects of ecstasy use on executive functions (Tables 4 & 5) have produced mixed and often contradictory results. Wareing et al. (2000) suggest that ecstasy users may have difficulty coping with tasks requiring high levels of cognitive demand. They investigated processes involving executive functions, specifically those related to Baddeley's (1996a) working memory component, the central executive. They compared 10 non-users, 10 current users and 10 previous users (abstinent for at least 6 months). The participants were tested on word span, Brook's Spatial Matrix task (a visual memory task) and a verbal memory task but as no significant differences were observed, there was no further discussion of these tasks. The Random Letter Generation task (Baddeley, 1996b) and a test of information processing speed were administered as tests of central executive function. Vowel intrusion and redundancy (repeating letters) in the random letter generation task were considered to be indicative of poor central executive functioning. The results showed higher levels of vowel intrusion at all generation rates (4s, 2s and 1s intervals) in the user groups. However, *redundancy* was only higher in the users groups at the quickest and most difficult generation rate (1s). The information processing speed stimuli were categorised according to the number of letters: 3, 6 or 9 stimuli. The users showed similar processing speeds to the controls, but with the 9 letter stimuli made more errors. The authors suggest these results show that ecstasy users have deficits on tasks which are demanding on cognitive resources, and that there is no evidence for recovery following abstinence. However, it is important to consider that the control group used in the study had no previous use of any recreational drugs, and that the previous users showed higher usage of LSD, cannabis and amphetamines than the current user group. A self-report health measure was also taken in which controls rated themselves as being in better health than both groups of ecstasy users. Both groups of users also scored higher for state anxiety. All these factors may have confounded the results. A more recent study by the same group revealed no difference in performance of random letter generation between ecstasy users and controls (Fisk et al., 2004). This study had a much larger sample size.

Zakzanis & Young (2001a) also argue that although much of the research has found evidence of episodic memory deficits, the underlying factor could be a higher order deficit related to serotonergic damage in the frontal lobes caused by MDMA use. They compared 24 ecstasy users who had been abstinent for at least 2 weeks, with 24 controls who had had some experience of other recreational drugs. The groups were compared on their performance of the Behavioural Assessment of Dysexecutive Syndrome (BADS; Wilson, 1995). This is a complex test designed to evaluate the 'Dysexecutive Syndrome', caused by various aetiologies and with varying degree of severity. There are six sub-tests that evaluate aspects of executive functioning. Zakzanis & Young (2001a) reported that ecstasy users performed worse that the control group on two of the six sub-tests, and that their overall score was significantly lower, indicating a trend for poorer performance throughout. The two tests were the Temporal Judgement Test, in which participants were required to estimate the time required to complete four common events (e.g. "How long is a visit to the dentist?); and the Modified Six Elements Test, in which participants had to complete at least part of six different tasks whilst adhering to various rules and restrictions. Negative correlations were found between performance on the tests and frequency, duration and usual dose of ecstasy. These results led the authors to conclude that an association exists between MDMA use and executive function deficits. They also suggest that the results could reflect changes in serotonergic function in the frontal lobes following MDMA use. They do, however, concede that the correlations may be flawed due to the unreliability of self-reported measure of ecstasy use. Due to the discrepancies between the two groups on levels of use of other recreational drugs, it is also impossible to rule out the possibility that deficits in executive function are more related to poly-drug use. 96% of the ecstasy groups used cannabis, compared to 63% of the control group, a pattern that was similar for amphetamines, cocaine, LSD, alcohol and cigarettes. This is particularly relevant as deficits in executive function have been found in participants with heavy cocaine, alcohol and cannabis use. In addition, no measure of impulsivity was administered, a trait that could affect performance on executive function tasks involving planning.

TEST		AUTHOR	√ – exstasy users impaired O - no group differences
Digit span	Forward	Croft et al. (2001)	√ vs controls O vs cannabis users
		Gouzouliz-Mayfrank et al. (2000)	O
		Rodgers (2000)	O
		Hanson & Luciana (2004)	O
		Dafters et al. (2004)	O
		Wareing et al. (2004a)	O
		McCardle et al. (2004)	O
		Wareing et al. (2005)	O
		Yip & Lee (2005b)	O
	Backward	Croft et al. (2001)	√ vs controls O vs cannabis users
		Gouzouliz-Mayfrank et al. (2000)	√ vs controls O vs cannabis users
		Rodgers (2000)	O
		Bhattachary & Powell (2001)	O
		Thomasius et al. (2003)	O
		Gouzouliz-Mayfrank et al. (2003)	O
		Hanson & Luciana (2004)	O
		McCardle et al. (2004)	O
		Yip & Lee (2005b)	O
Spatial working memory		Fox et al. (2002)	√
		Fox et al. (2001a)	√
		Hanson & Luciana (2004)	√
		Wareing et al. (2004b)	√
		Wareing et al. (2005)	√
		Roiser et al. (2005b)	O
Spatial span		Morgan (1998)	O
		Rodgers (2000)	O
		Gouzouliz-Mayfrank et al. (2000)	O
		Verkes et al. (2001)	√
		Bhattachary & Powell (2001)	O
		Wareing et al. (2005)	O
N-Back		Daumann et al. (2003b)	O
		Daumann et al. (2003a)	O
Matching to sample		McCann et al. (1999b)	O
Serial add & subtract		McCann et al. (1999b)	√
		Morgan et al. (2002b)	√ vs controls O vs cannabis users
		Curran & Verheyden (2003)	√ (ex-users only)
Rapid Visual Information Processing		Curran & Verheyden (2003)	√ (ex-users only)
WM sub-scales of WMS-R		Simon & Mattick (2002)	O
Computation span		Wareing et al. (2004a)	√
		Fisk et al. (2004)	√
		Wareing et al. (2005)	O
Delayed Match to Sample		Roiser et al. (2005b)	O

Table 1.4: Comparisons of ecstasy users and controls on tasks tapping working memory (WM)

TEST	AUTHOR	√ – ecstasy users impaired O - No group differences
Verbal fluency	Wareing et al. (2000)	O
	Gouzouliz-Mayfrank et al. (2000)	O
	Hefferman et al. (2001)	√
	Croft et al. (2001)	√
	Fox et al. (2002)	O
	Bhattachary & Powell (2001)	√ (not novice users)
	Morgan et al. (2002b)	O
	Curran & Verheyden (2003)	O
	Hanson & Luciana (2004)	√ (omission errors only)
	Yip & Lee (2005b)	√
Random letter generation	Wareing et al. (2000)	√
Tower of London	Morgan (1998)	O
	Morgan (1999)	O
	Fox et al. (2002)	O
	Fox et al. (2001a)	√ (planning time only)
	von Geusau et al. (2004)	√ (males only)
Go/No go	Gouzouliz-Mayfrank et al. (2000)	√
	Fox et al. (2002)	O
	Thomasius et al. (2003)	O
	Gouzouliz-Mayfrank et al. (2003)	O
Intra-dimensional / Extra-dimensional shifting	Fox et al. (2002)	O
Rule shift card sort	Fox et al. (2001a)	O
	Thomasius et al. (2003)	√ (preservative errors only)
	von Geusau et al. (2004)	√ (males only)
	Dafters et al. (2004)	O
	Lamers et al. (2006)	O
Digit cancellation	Morgan et al. (2002b)	O
	Curran & Verheyden (2003)	O
Digit symbol substitution	McCann et al. (1999b)	√
	McCardle et al. (2004)	O
	Yip & Lee (2005b)	√
Trail making test B	Thomasius et al. (2003)	O
	Morgan et al. (2002b)	O
	McCardle et al. (2004)	O
	Lamers et al. (2006)	O
Behavioural Assessment of Dysexecutive Syndrome (BADS)	Zakzanis & Young (2001a)	√ (Temporal judgement & modified six elements)
Paired associates learning	Rodgers (2000)	O
	Croft et al. (2001)	√ vs controls O vs cannabis users
	Fox et al. (2002)	O
	Gouzouliz-Mayfrank et al. (2003)	√ (delayed only)
	Montgomery et al. (2005)	√
	Daumann et al. (2005)	

Table 1.5: Comparisons of ecstasy users and controls on tasks tapping other 'executive functions'

Morgan (1998) used the 'Tower of London' (TOL), a planning task, to investigate executive function in ecstasy users. He carried out two studies comparing ecstasy users, poly-drug controls and non-drug using controls, and combined the results. He found no significant group differences on any of the measures of performance on the TOL test between the groups. There was a trend found toward increased 'initial thinking time' in the non-user group that could be interpreted as showing greater impulsivity in the drug using groups. Other studies have also found no evidence of impairment in ecstasy users on the TOL (Fox et al., 2002; Morgan, 1999).

Wareing et al. (2005) investigated both verbal and visual working memory in 36 current ecstasy users, 12 ex-users (abstinent for a minimum of 6 months) and 31 control participants. Verbal working memory was assessed using a computation span task involving participants completing a series of simple arithmetic problems whilst concurrently remembering the second digit in each problem. The authors claimed to have designed a visual working memory task that corresponded with the verbal task in that it also required simultaneous processing and storage of information. They found impaired visuo-spatial working memory in both ecstasy groups, while computation span was preserved (although the same group found evidence of impaired computation span in another study; Wareing et al., 2004a). The authors explain this discrepancy using Baddeley's (1986) three component model of working memory suggesting that verbal processing is dependent on a phonological system independent of the visuo-spatial system. Other studies have also found impaired spatial working memory (Hanson & Luciana, 2004; Wareing et al., 2004b).

One explanation for the variety of memory and central executive deficits seen in ecstasy users is provided by Zakzanis et al. (2002). They suggest that the pattern of deficits could be due problems involving a "supervisory attentional system". In order to investigate this possibility, Zakzanis et al. (2002) compared 24 ecstasy users with 30 controls on the Test of Everyday Attention (TEA). This test uses familiar everyday material to investigate selective attention, sustained attention, attentional switching and divided attention. The ecstasy users performed significantly worse than the control group on only one of the 8 sub-tests, the Map

Search 2. In Map Search 1 the participants are required to scan a map on an area and circle as many symbols (e.g. petrol station) as they can in one minute. In Map Search 2 they are required to use a different coloured pen to circle as many remaining symbols as they can in another minute. Interestingly the ecstasy group performed slightly better than controls on four of the eight sub-tests. A relationship was found between several of the tests and lifetime dosage of ecstasy. The number of times ecstasy had been used ranged from 2-100 occasions. If the majority of the ecstasy users were in the lower end of this range, it could account of the lack of difference between the groups. However, once again the problem of inaccurate self-reported drug histories must be taken into account; the authors themselves admit that it is a "notoriously unreliable" measure of drug-taking habits. Zakzanis et al. (2002) also concede that the attentional deficits observed may be related to poly-drug use rather than to MDMA itself.

Fox et al. (2002) investigated the neuropsychological profile of ecstasy users using a variety of tests that have been found to show impairments in ecstasy users, clinical patients with neuropsychiatric disorders involving serotonergic dysfunction and patients with frontal lobe damage. Their rationale was based on animal data showing damage to the serotonergic system, particularly in the frontal regions of the brain. Ecstasy users (abstinent for 2 weeks) were compared with poly-drug controls. There were no significant differences between the groups on the TOL and tests designed to tap ability to shift between rules, and the Go/No go task showed that there were no differences in ability to inhibit responses. Executive problems were, however, still apparent. The ecstasy users showed evidence of slightly worse performance than controls in relation to acquiring a reverse rule, and performed significantly worse than controls on a test of verbal fluency. The authors indicate that the failure to find more evidence of executive function deficits could be due to lower levels of ecstasy use reported by the participants in the current study. Other studies have, however, found no evidence of impaired verbal fluency (see Table 1.4).

Gouzouliz-Mayfrank et al. (2003) found a similar pattern of results to Fox et al. (2002) in that ecstasy users were impaired on tests of verbal memory, whereas their performance on tests of executive control, working memory and planning were

relatively unimpaired. The authors put forward a similar explanation to Fox et al. (2002), concluding that the pattern of results could indicate ecstasy induced neurotoxicity to the serotonergic system. They suggest that the hippocampus, which is linked to memory processes, may be vulnerable to this type of neurotoxicity as recovery of serotonergic function in this area as been shown to be relatively slow in comparison to other areas in animal studies (Hatzidimitriou et al., 1999). This is interesting when considering 2 recent MRI investigations (Daumann et al., 2005; Jacobsen et al., 2004) that have found different levels of activation in the hippocampus of ecstasy users compared to controls while performing a cognitive task (see section 1.8.7).

Interestingly, some evidence has been found of gender differences in executive function impairments following ecstasy use. Von Geusau et al. (2004) found that male ecstasy users were impaired on a range of tests tapping executive functions compared to controls, whereas female ecstasy users showed no impairments (see section 1.10)

1.8.7 Magnetic resonance imaging investigations of cognitive function in ecstasy users

Functional Magnetic Resonance Imaging (fMRI) has been used to assess brain activation in ecstasy users during cognitive task performance. Daumann et al. (2003b) used fMRI employing a blood oxygenation level-dependent (BOLD) contrast to compare ecstasy users and controls during an n-back task. Although no difference in cognitive performance was observed, greater activation was found in ecstasy users at the 1-back and 2-back levels of the task. Interestingly, this difference was only apparent in 'pure' ecstasy users and not those who used other recreational drugs. Moeller et al. (2004) also found greater activation in ecstasy users during a delayed memory task, although again performance on the task did not differ. BOLD response compares the change in activation between resting state and active state during a task. Thus, a greater response in the absence of behavioural differences could reflect the need for more neuronal activity to perform at the same level. This compensatory activation could be a possible explanation for the lack of

differences in cognitive performance often seen between ecstasy users and controls. However, the control group used by Moeller et al. (2004) was drug naïve making conclusions about the effects of ecstasy use alone difficult. In addition, out of the 15 ecstasy using participants 6 tested positive in their urine for cocaine and 2 for amphetamines and MDMA. It is plausible that the results partly reflect the acute effects of these drugs rather than long-term changes caused by ecstasy use. Jacobsen et al. (2004) found greater activation in the hippocampus of adolescent ecstasy users during an auditory n-back task. They suggested that the fact that the ecstasy users had only used between 1-25 ecstasy tablets (fewer than usually reported in investigations of adult ecstasy users) could indicate an increased sensitivity to MDMA-induced damage in adolescence. Results found by Daumann et al. (2005) were in concordance with those found by Jacobsen et al. (2004) in that both found evidence of alterations in hippocampal activity in ecstasy users. This is particularly interesting given the recent suggestion than memory impairments observed in ecstasy users could be indicative of hippocampal damage.

Daumann et al. (2004a) carried out a longitudinal investigation on 17 ecstasy users who were scanned during an n-back task at 2 test sessions 18 months apart. During that time, 8 reported complete abstinence from ecstasy and 9 had continued use. No differences were observed between the groups at baseline or follow up in n-back performance or activation. In addition, the abstinent users showed no significant change between the test sessions. However, increased activation in the parietal cortex was found at follow up in those who had continued ecstasy use. The authors suggest that these results indicate that there is no evidence of recovery over time. However, as there is no control group it is not possible to claim that the ecstasy users in the present study had different patterns of activation to non-ecstasy users at baseline. The increases in activation in the continuing users could, however, be interpreted as evidence of compensatory processes possibly due to cumulative damage caused by ecstasy use.

Although these studies appear to provide evidence of difference in neuronal activation during cognitive tasks, it is important to note that in all studies the ecstasy users showed the same pattern of activation as would be expected in healthy volunteers during the tasks they were performing.

1.8.8 Summary of the long-term effects of ecstasy use on cognitive function

From Tables 3, 4 and 5 it is apparent that the numerous findings relating to cognitive function in ecstasy users are far from consistent. Tests of executive function are, more often than not, unimpaired (see Table 5) and a similar pattern is apparent for working memory deficits (Table 4). Psychomotor and attentional tasks, such as simple or choice reaction time and Stroop, are generally unimpaired. One of the most consistent findings is that of deficits in verbal memory, particularly in immediate and delayed recall of prose and word lists. Even these tests have shown a great deal of variation between studies (see Table 3). In fact, more recent studies that have attempted to match control groups with MDMA users on factors such as age, premorbid IQ and, perhaps most importantly, use of other drugs such as cannabis, have found no differences between poly-drug users and MDMA users (Curran & Verheyden, 2003; Thomasius et al., 2003). These same studies have also found the intriguing pattern of impaired cognitive function in ex-users and not current users, as well as some preliminary evidence of gender differences in the effects of MDMA use. fMRI investigations have found differences in neuronal activity in ecstasy users compared to controls in the absence of differences in cognitive performance, suggesting a compensatory mechanism where by the ecstasy users show more activity to perform at the same level as drug-naïve controls.

Many studies have attempted to provide evidence that MDMA use causes cognitive deficits by correlating impairment with lifetime ecstasy use. However, estimates of lifetime use are highly unreliable, and thus any correlation based on it is flawed. In addition, many authors attempt to attribute cognitive deficits to MDMA-induced neurotoxicity. In animal studies, which are controlled and have none of the confounds present in studies of recreational users, no evidence of behavioural alterations are found, even after doses that lead to neurotoxicity that is still evident years later. In humans, on the other hand, many different cognitive deficits have been attributed to MDMA use. Cole et al. (2002b) conclude that there is a more complex mechanism behind the cognitive deficits observed in recreational MDMA users than simply MDMA-induced serotonergic neurotoxicity.

1.8.9 Long-term effects of ecstasy use on psychiatric symptoms and mood

As serotonin is thought to play a role in many psychiatric disorders, the prevalence of a range of disorders and symptoms has been investigated in ecstasy users. There are many documented case studies describing patients who have developed psychiatric symptoms after taking ecstasy (e.g. McCann & Ricaurte, 1991). However, case studies report individuals who have problems severe enough to be referred to or to seek help from clinicians and are therefore unrepresentative of the majority of the ecstasy using population who never seek clinical help. As an extensive history of the use of other drugs is often present, it is impossible to separate out any specific causal role of MDMA. Of the 26 case studies reviewed by Soar et al. (2001) 24% of the patients had previously diagnosed psychiatric illness, and 34% had evidence of family psychiatric history. The authors claim this is evidence for the relationship between MDMA and psychiatric illness. However, it is necessary to remember that, even if it has not fully manifested itself, there is a strong possibility that the disorder was present before the onset of ecstasy use, especially as poor premorbid adjustment is associated with drug use. It is possible that in these cases patients 'self-medicate' with illicit drug use to alleviate the distress caused by premorbid psychiatric disorders (Morgan, 2000). Soar et al. (2001) did not take into account the fact that the average age of the patients was 24 years old, within the age range when it is most likely for a first psychiatric episode to occur. It may well be the case that these patients had some sort of genetic predisposition to psychiatric illness. Jansen (2001) notes that psychotic episodes can be triggered by emotional experiences and that ecstasy use produces an 'emotional' experience. Cannabis use has recently been associated with psychotic symptoms (Fergusson et al., 2006), yet levels of cannabis use were not reported in the review paper by Soar et al. (2001). Given that, by Soar et al.'s (2001) estimation, 5 million people in the UK have tried ecstasy, the relatively small numbers of psychiatric cases reported indicate that it is highly unlikely that MDMA is directly causal.

In the largest study of psychiatric cases to date, Schifano et al. (1998) investigated 150 ecstasy users who had presented at an addiction treatment centre and found that 53% of the sample experienced one or more psychopathological problems including

psychotic disorders, social phobia, panic attacks, bulimic episodes and impulse dyscontrol. They also found that those with more psychopathological disturbances had a younger onset of ecstasy use and a greater lifetime dosage and thus claimed that these symptoms could be related to serotonergic neurotoxicity caused by MDMA use. However, once again this is a sample that tells us very little about the majority of recreational users who take ecstasy regularly with no apparent psychological sequelae. The participants in this study had all presented with drug addiction problems, thus are more likely to exhibit psychiatric disorders. Further, those identified as having psychopathological symptoms not only consumed more ecstasy tablets than those who did not, they also took more opiates (78% compared to 41%), more cocaine and more cannabis. All the participants were poly-drug users so the disturbances cannot be attributed to their ecstasy use alone. In reality, this study is more representative of psychological problems apparent in problem poly-drug users (those who were aware enough of their problem to refer themselves for psychiatric evaluation), rather than recreational ecstasy users.

Other studies have attempted to investigate psychiatric symptoms in recreational users who do not seek professional help. Parrott et al. (2000) carried out a study in Ireland investigating the self-reported 'psychobiological' problems associated with heavy ecstasy use. They administered the SCL-90, a clinical self-rating scale designed for use with psychiatric outpatients which has several sub-scales including anger-hostility, phobic-anxiety, depression etc, to 12 heavy users (who had used ecstasy on over 20 occasions), 16 light users (under 20 occasion) and 22 non-user controls. The results showed that the heavy ecstasy users reported significantly higher scores than controls on factors including obsessionality, anxiety, hostility, phobic-anxiety, paranoid ideation, psychoticism, poor appetite and restless/disturbed sleep. Light users showed increased scores compared to controls on just two scales: paranoid ideation and psychoticism. However, the authors note that the light users produced intermediate scores on many of the scales, an indication that the problems seen in the heavy users were starting to develop. It is a possibility, however, that pre-morbid psychiatric disorders were apparent within the group, but as yet had not been identified by the individual or others. Once again the participants were in their early twenties, a time when the onset of psychotic symptoms is most frequent. Little information is provided about levels of use of,

length of abstinence from, other recreational drugs. This is particularly important as two of the scales found to be higher in ecstasy users were those for poor appetite and restless/disturbed sleep, both of which are well known sub-acute effects of ecstasy. The disturbances in sleep patterns have been found in ecstasy users (Allen et al., 1993), and differences in food intake are have been observed for a week after ecstasy ingestion (Turner et al., 1998). Interestingly, no differences were found between the groups on the uplifts, hassles, stresses and cognitive failures questionnaire, which is a subjective measure of the relative frequency of these events. This indicates that the participants' experiences of everyday life were similar, which seems unusual considering the high scores on several scales of psychological symptoms shown by the heavy users group.

Parrott et al. (2001) found similar results using the same scale in a larger study involving 768 young people from Italy and England. Again, there is no background information about the participants and none were screened for previous psychiatric illness, so it is impossible to rule out the possibility that pre-existing problems may have influenced the results. The authors claim that this is unlikely. They cite the example of phobic anxiety, one of the scales that becomes higher as poly-drug use increases, and claim that it is very unlikely that a person with a social phobia would take ecstasy and go to a crowded club or rave. On the contrary, it could be argued that, as MDMA induces euphoria and a feeling of closeness to others it could be the perfect drug for someone with a social phobia to self-medicate and release themselves temporarily from their phobia. Cole et al. (2002d) criticise this study in relation to the choice of scale used. They point out that the SCL-90 is an incomplete version of the SCL-90-R. Derogatis (1994), the author of the scale, found that "item analysis of the original SCL-90 revealed items on the anxiety and obsessive-compulsive dimensions were flawed psychometrically". Although interesting suggestions might be made about poly-drug use, it is impossible to extract information about the effects of MDMA alone from this data as MDMA use and use of other drugs increased in parallel.

A study by Thomasius et al. (2003) highlights the importance of controlling for the use of other recreational drugs. They administered the SCL-90-R to 30 current ecstasy users, 31 ex-ecstasy users (at least 5 months abstinence), 29 poly-drug

controls and 30 drug-naïve controls, as well as a battery of cognitive tests and a PET scan assessing serotonin transporter density (see sections 3.1 and 1.8.5). They found elevated scores on several of the sub-scales in all drug-using groups compared to the controls, although there were no differences between current and ex-ecstasy users compared to poly-drug controls indicating that increased levels of psychopathology is more likely to be related to drug use in general rather than ecstasy user *per se*. With the same participants, Thomasius et al. (2005) also assessed lifetime prevalence of psychiatric disorders as outlined in the DSM-IV. There were no significant differences in prevalence between ecstasy using groups and the poly-drug controls, while the only disorder to reach significance when comparing drug-using groups to controls was Attention Deficit Hyperactivity Disorder (ADHD).

1.8.9(i) Depression

The role of serotonin dysfunction in depression (see section 1.5.1) has prompted research to investigate prevalence of depression among ecstasy users. Verheyden et al. (2003a) reported that 37.4% of participants interviewed about their experiences of ecstasy use reported feeling depressed as a long-term effect of the drug. Gerra et al. (2000b) compared 15 male ecstasy users with 15 controls, and tested them 3 weeks and 12 months after giving up the drug. They found that ecstasy users had higher levels of depression than controls at both 3 weeks and 12 months after cessation of ecstasy use. However, the ecstasy using group were selected from males who contacted a drug rehabilitation centre and were clearly not matched to the control group (see section 1.9.3). It is possible that increased depression is related to the life situation of the group rather than a result of MDMA-induced 5-HT neurotoxicity. Increased depression scores could be expected in a group who have acknowledged they have a problem with drug abuse and who have to attend a rehabilitation clinic regularly. This is supported by the high levels of guilt reported by the participants, probably also connected to their need for rehabilitation. Verkes et al. (2001) found slightly increased scores on the BDI when comparing heavy and moderate ecstasy users with non-using controls all recruited from with the dance scene in Holland. The differences observed did not reach significance and could be explained by other factors such as the greater usage of cannabis and cocaine within the heavy ecstasy using group, and the fact that some of the ecstasy using

participants had taken the drug 2 days before the study. In fact, the average abstinence time for the heavy ecstasy users was only 9 days, arguable not long enough to ensure results are not being caused by the sub-acute effects of the drug.

Morgan (1998) compared 25 ecstasy users, 20 poly-drug controls and 19 non-drug controls using the General Health Questionnaire (GHQ, Goldberg, 1978), a brief questionnaire measure of current psychological health status. Although the ecstasy group showed significantly higher GHQ scores than the non-drug control group, there was no significant differences between the ecstasy group and the poly-drug control group. Once again, the evidence seems to indicate that lower psychological health scores stem more from drug use in general rather than MDMA use specifically. This hypothesis is supported by an investigation into the subjective experience of negative long-term effects of MDMA. Williamson et al. (1997) conducted interviews with 158 current drug users and found that similar numbers of ecstasy and cocaine using participants reported experiencing depression and anxiety, whereas higher numbers of amphetamine using participants reported experiencing these and other mental health problems. Both of these stimulants are often used concomitantly with ecstasy, so to separate out their effects is difficult.

MacInnes et al. (2001) investigated depression in former chronic ecstasy users. All 29 of their participants had consumed over 100 ecstasy tablets, with 31% having taken over 700. They had not used the drug for an average of 26 weeks. They found that the user group had a significantly higher BDI scores (9.3 vs 5.2) than a control group matched for age, sex and educational level. The ecstasy group also completed a Locus of Control scale (Rotter, 1966), a Daily Hassles scale and Life Stress Units were calculated for each participant. Scores on all three scales unsuprisingly correlated with BDI scores, and female participants had higher life stress units and locus of control scores. BDI scores correlated with 'maximum tablets consumed in 12 hours' and daily hassles scores, but not life-time consumption of ecstasy tablets. The authors claim that the chronic users in this study fit the 'vulnerability' model of depression, and therefore may be more at risk of developing more severe depressive symptoms than controls. It is possible that scores on the Daily Hassles scale and the Life Stress Units represent a pre-existing vulnerability to depression caused by life stress or a more external locus of control.

However, as these scales were not administered to the control group, it is difficult to draw any comparisons. In the ecstasy using group, 66% were currently using cannabis, 13% amphetamines and one heroin and ketamine, whereas no previous drug use was reported for the control group. Cole & Sumnall (2002) point out that although the ecstasy group had slightly elevated BDI scores, they are within the range of scores found in other healthy, non-drug using populations. In fact, a score of 16 or more on the BDI is usually considered to indicate clinical depression, while 12-14 indicates mild depression. This point also applies to other studies who report significant differences between ecstasy users and controls on the BDI while in fact the users' scores indicate they are not depressed (e.g. de Win et al., 2004; Hanson & Luciana, 2004). A recent report by Falck et al. (2005) found that of the 402 young ecstasy users who completed the BDI-II (2nd edition of the BDI), scores of 75.6% placed them in the non-depressed/minimal depression category, while only 4.7% scores high enough to imply severe depression. They also found that gender and opiate use were strong predictors of depression, while ecstasy use failed to reach significance in a regression analysis.

Jansen (2001) comments that depression is predicted as an outcome of taking MDMA on theoretical grounds due to the link between serotonin and depression (see section 1.3.1). In fact, anxiety appears to be more frequently reported than depression. For example, Parrott et al. (2000; 2001) report that heavy ecstasy users score significantly higher on the phobic-anxiety scale of the SCL-90, whereas depression scores do not differ. However, Morgan (1998) found no differences in levels of trait anxiety on the Spielberger Trait Anxiety Inventory (STAI) between ecstasy users and controls with no use of psychoactive drugs. As discussed in section 1.8.2, it is possible that people with depression are more likely to take ecstasy in order to self-medicate, to experience elevated mood and positivity in contrast to their depressive symptoms.

In a recent meta-analysis of 25 studies that investigate depression in ecstasy users, Sumnall & Cole (2005) conclude that although there is an association between ecstasy use and depressive symptoms, it is weak. They also point out than many of the studies included in the analysis fail to control for the use of other recreational drugs. Overall, evidence regarding the effects of ecstasy use on depression has

been mixed. While some studies controlling for poly-drug use have not found differences in depression specific to ecstasy use (Roiser & Sahakian, 2005), others have (Thomasius et al., 2003).

1.8.9(ii) Impulsivity

Low levels of serotonin have been associated with impulsive personalities and serotonin deficits have been observed in novelty-seeking individuals (Zuckerman et al., 1988). Thus it has been proposed that the use of MDMA could lead to more impulsive personality traits. Morgan (1998) measured impulsivity using the Impulsiveness, Venturesomeness & Empathy scale (IVE, Eysenck & Eysenck, 1991). There were no significant differences when compared to the poly-drug control, indicating that increased impulsivity is associated with illicit drug taking in general rather than it being caused by taking ecstasy.

An early study by McCann et al. (1994) found that ecstasy users exhibited *less* impulsivity on the Multidimentional Personality Questionnaire compared to controls. Since then, the authors claim to have found evidence of increased impulsivity in ecstasy users in unpublished data (McCann et al., 2000) and have attributed this early finding to changes in pattern of ecstasy use. They claim that recreational ecstasy users in the original study took the drug more sporadically than those who take it now. However, comparing the characteristics of ecstasy use for participants in the 1994 study and those investigated by Morgan (1998), there is very little difference in patterns of ecstasy use; the duration of use for both groups is approximately 4 years, frequency of use per month is just over four in both studies and average dosage in each occasion is 1-2 tablets.

Gerra et al. (2000b) found higher levels of novelty seeking behaviours at both 3 and 12 weeks after cessation of ecstasy use. The authors suggest that this behaviour is a pre-existing trait as it is unaffected by long periods of abstinence. This idea is supported by Curran & Verheyden (2003) who found that both current and ex-ecstasy users (abstinent for at least 1 year) showed higher levels of impulsivity than poly-drug controls.

Parrott et al. (2000) found evidence that heavy ecstasy users exhibited higher levels of Impulsivity on the IVE scale compared to poly-drug using controls. They argued that this difference was likely to reflect a reduction in serotonin function, rather than a pre-existing difference. They do, however, concede that as the levels of other recreational drugs was much higher in the heavy user group, it is possibile that this impulsivity is simply a characteristic of *heavy* recreational drug users. This idea is supported by the results of a study comparing ecstasy users with both cannabis using and drug-naïve controls. Dughiero et al. (2001) found that the ecstasy users showed higher scores on the novelty-seeking dimension of the Three-Dimensional Personality Questionnaire compared to both control groups. Once again, the ecstasy group were much more likely to have taken large quantities of other recreational drugs than both control groups.

Tuchtenhagen et al. (2000) compared 28 ecstasy users with two control groups; one matched for cannabis use and another group with no previous illicit drug experience. They found that the ecstasy group exhibited higher scores than both control groups on the non-planning subscale of the Barrett Impulsivity Scale (BIS) and on the experience seeking subscale of the Sensation Seeking Scale (SSS-V). However, both drug-taking groups had higher global scores for the SSS-V. The difference between the drug taking groups in the two subscales could have arisen due to the short abstinence period of 7 days that was required for the study. Walderhaug et al. (2002) found that lowering of serotonin by rapid tryptophan depletion increased impulsiveness in 24 healthy male volunteers with no history of drug use. Thus, the increase in impulsiveness observed here may be due to a temporary depletion of serotonin after the last MDMA experience, rather than a long-term alteration of the serotonergic system. The importance of matching groups for the use of other drugs is highlighted by Butler & Montgomery (2004) who administered the IVE and the Tri-Dimensional Personality Questionnaire (TPQ) to 254 students with a range of drug use found that while both heavy (>20 occasions) and light (<20 occasions) ecstasy users as well as poly-drug controls scored higher than drug-naïve controls on impulsiveness and venturesomeness (IVE) and on novelty seeking (TPQ), there were no significant differences between these drug-using groups.

As the reliability of self-report measures can be uncertain, behavioural measures of impulsivity have also been used to assess ecstasy users, with mixed results. Tests of response inhibition such as the Go/No Go have generally been found to be unimpaired (e.g. Gouzouliz-Mayfrank et al., 2003). Ecstasy users have been found to be respond more impulsively on the Matching Familiar Figures (MFF) task in some studies (Morgan, 1998; Morgan et al., 2002b; Morgan et al., 2005) but not others (Dafters et al., 2004). A decision making task has also been used to assess how information about the probability of losses and gains are used to make responses. Again, the results are mixed with one study finding evidence that ecstasy users show reduced discrimination between sizes of gains and losses when making 'risky' (or more impulsive) decisions (Morgan et al., 2005), while another study using the same task finds no significant differences (Roiser et al., 2005b).

In an interesting review of the psychiatric aspects of impulsivity, Moeller et al. (1994) discuss impulsivity in terms of a predisposition towards a pattern of behaviour that is connected to seeking immediate gratification with reduced regard for consequences of actions. It seems clear that of all the mood changes that have been linked to ecstasy use, impulsivity is the most likely to be a pre-existing trait. The type of behaviour described by Moeller et al. (1994) describes drug use behaviours of ecstasy users very well: they are aware of the risks associated with using the drug (Gamma et al., 2005) and yet still choose to take it to achieve the immediate reward of its positive acute effects.

1.8.9(iii) Aggression/hostility

Low levels of serotonin have also been linked to aggressive behaviour (see section 1.5.2), yet the human data does not appear to indicate long-term changes in aggressive behaviour after MDMA use. Evidence of aggression in ecstasy users is discussed fully in Chapter 5.

As discussed in section 1.8.1, there is evidence that increased aggression may be a sub-acute effect of MDMA. Verheyden et al. (2002) compared 40 regular ecstasy users with 40 poly-drug users on the night of drug use and four days later, and found increased aggression in ecstasy users mid-week. The authors attribute this to the temporary depletion of serotonin caused by the MDMA experience. This is

supported by the fact that there were no group differences in scores on the Aggression Questionnaire, which is thought to be a measure of trait aggression. Further evidence that increased levels of aggression found in ecstasy users is likely to reflect a temporary depletion of serotonin comes from studies that have lowered levels of serotonin in the brain using rapid tryptophan depletion. Cleare & Bond (1997) found an inverse relationship between levels of serotonin function and measures of aggression. Thus, a long abstinence period would be required to establish if aggression is a long-term outcome of MDMA use.

1.8.10 Summary of the psychiatric and mood effects of long-term ecstasy use

Evidence of ecstasy-users developing psychiatric problems often comes from case studies, or anecdotal descriptions of users. There is, however, no discussion of individuals who use ecstasy regularly and who show no evidence of psychiatric problems, even though this is far more representative of the majority of those who use the drug.

Many studies finding problems in ecstasy users also find that similar problems exist in poly-drug users (Parrott et al., 2001). Mood disturbances linked to 5-HT function have been investigated extensively in ecstasy users. Only a minority of studies have found evidence of increased depression, anxiety and aggression, although aggression has been found to be an element of the mid-week lowering of mood experienced after ecstasy use at the weekend. Impulsivity has also been identified in some studies as being higher in ecstasy-users compared to controls. However, as previously discussed, this is not surprising as people who use illicit drugs are more likely to have impulsive or sensation seeking personalities.

A major problem in attributing mood and psychiatric problems to ecstasy use is the possibility of premorbid differences. Poor premorbid adjustment is associated with increased drug use, and may be related to self-medication.

1.9 The role of cannabis in human ecstasy research

In many studies the use of cannabis is much higher in ecstasy using groups than in controls, even where attempts have been made to match the groups on poly drug use. Collin's (1997) book on rave culture describes the popularity of cannabis within the dance scene, with many users seeing it as a measure to alleviate both the negative acute effects and the mid-week low associated with weekend ecstasy use. In fact, studies have found 73 - 100% of ecstasy users in their samples also use cannabis (for review, see Sala & Braida, 2005). The drug use history information in many studies show that ecstasy users are generally chronic users of cannabis - for example Morgan's (1999) current ecstasy users smoked an average of 13.74 cannabis joints a week and had done so for an average of 6.14 years). The relevance of this is highlighted by studies that have shown that chronic cannabis use may produce deficits in cognitive functioning and differences from control subjects using imaging techniques such as fMRI (for review, see Lundqvist, 2005). In addition, Gouzouliz-Mayfrank et al. (2002) concluded that neuroendocrine response to fenfluramine appeared to be more strongly related to cannabis use that ecstasy use (see section 1.8.3(ii)). As much of the research investigating the functional consequences of the suspected neurotoxicity of MDMA has focused of various aspects of memory ability, it is possible that the observed deficits in memory arise from the concurrent use of cannabis. This is supported by results from studies such as Morgan (1999) which reported that cannabis consumption was negatively correlated with immediate recall in a similar way to ecstasy, suggesting that it is also playing an important role in observed deficits.

In an attempt to separate out the effects of cannabis and MDMA, Rodgers (2000) compared 15 ecstasy users (abstinent for 2 months) who were also habitual cannabis users (4 days a week for 10 years), with 15 cannabis users who had the same frequency and duration of use and 15 drug-naïve controls. Both drug-using groups reported being abstinent from cannabis for 1 month. All participants completed visual, auditory and complex reaction time tasks. All sub-scales of the Wechsler Memory Scale (Revised) were administered and index scores were calculated for verbal, visual and general memory, attention and concentration and delayed recall. They also completed the Cognitive Failures Questionnaire (Broadbent et al., 1982)

in which subjects had to self-rate their cognitive performance. A significant impairment was reported on both verbal and general memory for both the cannabis and the ecstasy using groups compared to the controls. The ecstasy using group showed worse performance on the delayed recall component compared to both the cannabis and the control groups. Further analysis showed that both cannabis and ecstasy users were impaired on the logical memory sub-test in both immediate and delayed recall. Similar results have been reported for ecstasy users (e.g. Morgan, 1999), yet in Rodgers' (2000) study, cannabis users also showed this decrement. The authors suggest that impaired immediate and delayed prose recall may be an outcome of long-term cannabis use rather than ecstasy use. However, the delayed recall index, which comprises both a verbal and a visual element was impaired only in ecstasy users. The authors argue that this indicates that the concomitant ecstasy use could cause deficits in a wider range of delayed recall abilities. It was also found that there were no differences between groups in regard to their self-assessment of cognitive failures. The author suggests that this could be a result of the questionnaire lacking sensitivity, but it is more likely that the deficits observed are not apparent in everyday functioning.

Croft et al. (2001) also attempted to separate out the relative contributions of cannabis and MDMA to cognitive impairment and, like Rodgers (2000), compared ecstasy/cannabis users, cannabis users and drug-naïve controls. Cannabis consumption was similar across the drug-using groups. The participants abstained from ecstasy for at least 1 week, and from cannabis for 17 hours. The groups were compared on a battery of 18 cognitive tests, and the drug using groups differed significantly from controls on 8 of these tests. These deficits related to learning, memory, verbal word fluency, speed of processing and manual dexterity. Further analysis also showed that for the majority of tests no group differences were seen when frequency of use or lifetime use of ecstasy were used as covariates. On the other hand, covarying for cannabis consumption led to the loss of most significant differences. The authors therefore argue that previous studies have misattributed memory impairments to MDMA rather than cannabis use. It should be noted however, that the ecstasy/cannabis group in this study had relatively low ecstasy consumption compared to previous studies, a factor that may have caused the disparity between these results and those of previous studies.

Croft et al.'s (2001) suggestion that cannabis use may be a better predictor of memory performance than ecstasy use is supported by a study by Simon & Mattick 2002). They suggest that factors such as general intelligence or the concomitant use of cannabis have not been adequately controlled for in previous studies. They compared 40 regular ecstasy and cannabis users with 37 regular cannabis users on the Wechsler Memory Scale III and two tests of intelligence. They also performed a regression analysis to assess the value of ecstasy use, cannabis use and intelligence as predictors of memory performance. The regression analysis was undertaken due to the extremely broad range of consumption of ecstasy within the groups. No significant differences were found between the two groups on any measure of memory. They found that scores on the 'vocabulary' sub-scale (a measure of verbal intelligence shown to be relatively insensitive to neurotoxins such as lead and solvents, and thus a good estimate of pre-morbid intelligence) was an significant predictor for several of the memory scales, and that the level of current cannabis use only approached significance ($p=0.07$) as a predictor of delayed verbal memory. These results indicate the importance of matching groups for pre-morbid intelligence. The failure to replicate the finding of many previous studies in terms of memory deficits compared to controls may be due to the inclusion of very low ecstasy use within the control group. However, as the maximum dosage allowed for controls was 5 tablets, and the average dosage in the ecstasy group was 258, it appears that this explanation is unlikely. On the other hand, this average would only be 89 if one subject who reportedly had ingested 3583 tablets were excluded. It is also important to remember that the results could reflect residual effects of the drugs as the abstinence period for both ecstasy and cannabis was only 24 hours.

Contradictory results were found by Gouzouliz-Mayfrank et al. (2000) using a similar design to compare ecstasy/cannabis users with two control groups: a cannabis control and a control that used no illicit drugs. The authors recruited participants who used very low amounts of other psychotropic drugs. The three groups completed a battery of tests of memory, learning, attention, executive function and general intelligence. Although the ecstasy group were not heavy users (on average they consumed 3.5 doses per month) several significant deficits were

reported in their performance. They performed worse than both control groups on a Go/No go task, a test of visuo-spatial memory and on 3 tests of general intelligence. Furthermore, they performed worse than the drug-naïve control group on verbal working memory (digit span backwards) and immediate recall. Performance on several of these tests was associated with heavier ecstasy and cannabis use. In conclusion, the authors claim that the concomitant use of cannabis is unlikely to account for the deficits seen in the ecstasy group. Unusually, on the tests of divided attention and intermodal integration, the ecstasy group performed significantly worse than the cannabis group *but not* the control group. This is an unexpected result and may indicate that the cannabis group had above average performance. This problem may have been exacerbated by the fact that the ecstasy group performed worse on a test of general intelligence that is thought to remain stable, even with early cognitive deficits. However, when general knowledge was used as a covariate, significant group differences still remained, and all three intelligence tests were found to inter-correlate. On the other hand, it is important to consider that general knowledge may well not be a good indicator of pre-morbid IQ as it is highly influenced by education. It is also important to note that the abstinence period for ecstasy use was only 7 days.

Dafters et al. (2004) discuss the possible reasons for the conflicting results of these studies. They suggest that it reflects the two drugs causing different types of cognitive impairments, or alternatively that both could contribute to in an additive way to the same underlying memory deficit. They compare both 19 light (<50 tablets) and heavy (≥50 tablets) ecstasy users who also used cannabis with a cannabis control group and a drug-naïve control group. Initially, they found no significant differences between the groups. After combining all the drug using groups they found evidence of impaired immediate and delayed prose recall and free recall in all drug users compared to controls. There were no significant differences apparent on tests tapping executive function/attention (Wisconsin Card Sorting Task, digit span and the Visual Elevator, a sub-set of the TEA). They conclude that they have found no evidence that memory impairments are caused by ecstasy use *per se*.

The contribution of the effects of cannabis use, and that of other recreational drugs, to observed cognitive deficits in ecstasy users is still far from clear. Two recent studies clearly demonstrate this disparity. Roiser et al. (2005b) compared 30 current ecstasy users, 20 ex-users, 30 poly drug controls who were well matched for the use of other recreational drugs and 30 drug naïve controls. They found significant impairments in ecstasy users compared to controls on only 3 sub-scales of a wide battery of tests, and more importantly no significant differences in tests of working memory and planning (Tile Manipulation test, Mental Rotation test, Delayed Matching to Sample test) between the ecstasy using groups and the poly-drug controls. On the other hand, Yip & Lee (2005b) investigated a large group of ecstasy users (n=100) who reported no previous use of other recreational drugs, including alcohol and tobacco. This is an apparently unique group of ecstasy users who would be almost impossible to find in the UK. This study took place in Hong Kong where the use of ecstasy is a very recent phenomenon. They found significant impairments on tests of verbal and non-verbal memory and verbal fluency. No group differences were observed on tests of working memory and attention.

Halpern et al. (2004) were also able to test a seemingly unique group of ecstasy users who reported very little use of other drugs by recruiting in Salt Lake City in Utah, an extremely religious state. They recruited 23 ecstasy users who reported fewer than 50 episodes of drunkenness, fewer than 50 lifetime occasion of cannabis use and no use of other recreational drugs and compared them with 16 drug-naïve controls. In an initial comparison, they found very little difference in cognitive performance between the two groups. However, when they divided the ecstasy group into 12 moderate users (22-50 occasions) and 11 heavy users (60-450 occasions) they found group differences on tests including the Stroop test, spatial span, and the Wisconsin Card Sort Test (WCST). They authors claim that this is strong evidence of cognitive impairment caused by MDMA use, and that they appear to reflect frontal lobe damage. However, as argued by Lyvers & Hasking (2004), the possibility of obtaining a Type I error in a design which yields 39 separate measures is high, especially as there were only 39 participants in total. In addition, some of the significant results found failed to reach significant following adjustment for family origin. Although the use of other drugs was limited, the

ecstasy users still had significantly higher cannabis and alcohol use than the control group. Finally, it seems intuitive that it is particularly likely that people who choose to take recreational drugs in a social environment where it is strictly prohibited have pre-existing differences from those who do not.

An interesting picture has begun to emerge in the literature relating to the contribution of cannabis to the mood and psychiatric symptoms of ecstasy users. Daumann et al. (2001) attempted to separate out the effects of ecstasy from that of other recreational drugs by comparing an ecstasy group who used cannabis but who had very little experience of other drugs (no more than once a month), with a control group matched for cannabis use and a drug naïve controls group. They compared the three groups on a series of self-rating scales assessing aspects of personality associated with serotonin dysfunction: sensation seeking, impulsivity, aggression, anger, anxiety and depression. The ecstasy using group scored higher than the control group on the non-planning impulsiveness subscale of the BIS, and the cannabis using group scored higher than controls on the thrill & adventure subscale of the SSS-V. Cannabis users also showed slightly higher levels of aggression than the ecstasy using group. The most important finding here was that although there were a number of significant correlations between psychometric measures and previous use of both ecstasy and cannabis, the duration of cannabis use and age of onset of its use were particularly strongly associated with psychological problems. However, this purely correlational evidence does not imply causation.

Morgan et al. (2002b) found similar results. Both current and ex-ecstasy users showed elevated scores on the SCL-90-R compared to a poly-drug control group and a control group with no history of recreational drug use. Interestingly, whereas in the same study cognitive performance was predicted by previous ecstasy use, 'psychopathology' (as measured by the SCL-90-R) was best predicted by previous cannabis use.

The idea that cannabis may in fact be more related to psychopathological symptoms in ecstasy users while ecstasy contributes more to the cognitive deficits observed is supported by a longitudinal investigation carried out over 18 months by Daumann et

al. (2004b). On the first test session 60 ecstasy users were compared with 30 control participants and reported significantly more psychopathological symptoms. 18 months later, 38 of the ecstasy users were re-tested, 50% of whom had reported abstinence from ecstasy and 50% abstinence from cannabis. No differences were found between the 2 test sessions, and in addition no differences were found between those participants who had stopped using ecstasy and those who had continued. However, when comparing those who had stopped using cannabis with those who had not the authors found that those who reported continued cannabis use scored higher on every scale of the SCL-90-R at the follow up session. However, none of the control group were re-tested at the follow up session, and as 22 of the ecstasy users were not retested the possibility of a sampling bias means these results should be treated with some caution.

A longitudinal investigation following 3021 14-24 year olds confirmed previous findings that the use of other illicit drugs is higher in ecstasy users compared to those who take other recreational drugs (43.7% vs. 11.7%) (Lieb et al., 2002). This finding supports the notion that caution is required when attributing problems to MDMA alone in the presence of poly-drug use. They also found increased proportions of ecstasy users suffered from mental disorders, but interestingly, the results also indicated that in the majority of cases (88.4%) the onset of mental disorders occurred *prior* to the first use of ecstasy. In addition, those with a history of mental disorder appeared to have a higher incident of ecstasy use (6%) compared to those with no mental disorder (3.2%). However, it is important to remember that only 6.6% of the sample reported having ever used ecstasy.

A recent debate has focused on the possibility of far more complex interactions existing between MDMA and cannabis. When administered acutely with MDMA, Δ^9-tetrahydrocannabinal (THC, the psychoactive component of cannabis) partially prevents 5-HT depletion in rats (Morley et al., 2004). This has lead some to suggest that cannabis could also be neuroprotective in human ecstasy users. Parrott et al (2004) discuss this possibility, and cite studies investigating ecstasy users with counter-intuitive results. For example, Milani et al. (2005) found that ecstasy users with moderate cannabis use rated themselves as *less* aggressive than those who did not smoke cannabis, and Rodgers et al. (2003) found that in a group of ecstasy users

cannabis use was associated with fewer procedural memory errors (as assessed by self-report). Although both of these studies could be criticised for relying on self-report data, evidence to suggest differential consequences of using ecstasy alone rather than in combination with cannabis has also been found using fMRI. Daumann et al. (2003b) compared 8 'pure' ecstasy users with 8 ecstasy users who also reported the use of cannabis and amphetamines and a drug naïve control group on an n-back task and fMRI response to the task. Although no significant differences were observed in performance on the n-back task, pure ecstasy users had lower activation compared to controls during the 1-back condition, while the ecstasy users who also used other drugs did not differ. At the 2-back condition, the pure users had lover activation than *both* other groups. Although these results could be interpreted as implying reduced neurotoxic effects of MDMA when combined with other drugs, a great deal of research is needed to further clarify this issue, and it is likely that the interactions are extremely complex. One mechanism by which cannabis could be neuroprotective is its acute effects of lowering body temperature. As greater evidence of neurotoxicity is found in animals treated with MDMA in higher temperatures, cannabis could provide some protection form this. However, although this could be the case acutely, this is unlikely to provide any protection from chronic use, which is a better model of use in typical ecstasy users. During a spatial working memory task, habitual cannabis users have been found to have greater activation and to show activation in regions not typically associated with this type of task when compared to controls (Kanayama et al., 2004). Other neuroimaging techniques have also found significant differences between heavy cannabis users and controls (see Lundqvist, 2005, for review).

1.10 Is there any evidence of gender differences?

Very few studies have attempted to investigate whether there are gender differences in the effects of MDMA. McCann et al. (1994) carried out a study comparing ecstasy users with poly drug controls on measurements of CSF 5-HIAA concentration and various personality questionnaires. They found that the ecstasy users had significantly lower levels of CSF 5-HIAA than controls. Further, they found that female ecstasy users had lower concentrations compared to female

controls than male users had when compared to male controls (46% compared to 20% reduction). This is particularly interesting when compared to their finding that, within the control group, males showed lower levels of CSF 5-HIAA than females. However, it is important to remember that although total dosage of ecstasy taken by males and females within the ecstasy group were similar, the weight of the females was lower, indicating a higher dosage per kilogram that could account for the differences. Further analysis of the data also found that on average females had taken ecstasy on more occasions than males (115 versus 85). There was also little control over the quantity of ecstasy taken (due to self reported drug use histories), or its purity in relation to MDMA content. Although not reported as statistically significant, many more of the ecstasy group had used illicit drugs other than those in the control group (for example, 80% of the ecstasy group reported any prior use of cocaine, compared to only 29% of the control group).

The suggestion of greater serotonergic dysfunction in female ecstasy users, along with evidence of higher numbers of females suffering from depression and anxiety, may indicate that women may be more susceptible to alterations in serotonergic function. This idea prompted Liechti et al. (2001a) to investigate gender differences in a controlled study of the acute effects of MDMA. The study combined the results of three double-blind placebo controlled studies of the acute effects of MDMA. Overall, 54 male and 20 female participants were administered doses of MDMA ranging from 70 – 150 mg (1.35-1.8 mg/kg). Physiological measures including blood pressure, heart rate and body temperature were taken along with psychometric rating of the subjective effects of the drug. Analysis of the results revealed that female participants reported significantly higher increases in positive basic mood, depersonalisation and altered perception of space and time. They also reported more fear of loss of bodily control and more perceptual changes. In addition, females experienced more adverse effects of MDMA including jaw clenching, dry mouth and loss of appetite. They also found that sweating and nausea were more prevalent in men, which could be related to the fact that increases in body temperature were significant in men but not women. Increased blood pressure was also more pronounced in male participants. In addition, women more frequently reported short-term sequelae lasting up to 24 hour later, including fatigue, headache and emotional irritability. The authors argue that these results

provide evidence for pharmacodynamic gender differences in the effects of MDMA, which in turn could suggest that women are more susceptible to alterations in the serotonergic system. However, as blood plasma levels of MDMA were not measured in this experiment, it cannot be ruled out that women had higher blood levels of MDMA caused by pharmacokinetic gender differences. The authors reject this claim citing as evidence the greater rise in blood pressure in male participants, which would be unlikely if blood plasma levels of MDMA were lower in men. It is, however, more difficult to resolve the issue of whether or not these reported effects are actually stronger in women, or if they give higher self-report ratings for similar effects.

Verheyden et al. (2002) conducted a study to investigate the acute and sub-acute effects of MDMA examining participants in a party situation and 4 days later, with a further aim of determining whether there is any gender differences in these effects (see section 1.8.1). They found evidence that females who had used ecstasy at the weekend showed greater increases in depression scores (BDI) than male users, and that their depression scores were correlated with the dosage of ecstasy they had taken at the weekend. This increase was quite marked with the female users, with over one third scoring in the range for mild to moderate clinical depression. There were no gender differences in the increase in mid-week aggression, although only male participants showed a correlation between increases in aggression mid-week and number of ecstasy tablets taken on day 0. As this study suffers from all the methodological problems associated with other 'club studies' of ecstasy users, it is impossible to rule out the possibility that the female ecstasy users, although reporting a similar amount of tablets ingested on the night, could simply have consumed significantly more MDMA than the males. Although the authors report units of alcohol and amount of cannabis smoked by participants between the two tests sessions, they do not indicate whether participants had used other illicit drugs on the night. This is highly likely as ecstasy users often report concurrent use of other stimulants such as cocaine or amphetamine, or other drugs such as cannabis, ketamine and LSD. It would have to be established if there was any differences in consumption of other drugs before definite conclusions about gender differences in the sub-acute effects of MDMA could be drawn. The authors also point out that

further investigation is needed, taking into account the hormonal changes in women that occur in relation to the menstrual cycle.

Von Geusau et al. (2004) investigated cognitive function in 26 ecstasy users (17 males, 9 females) and 33 control subjects (12 males, 21 females). Although the ecstasy users were unimpaired on the majority of tests, a significant impairment was found in male ecstasy users on tests of cognitive flexibility. However, the fact that the male ecstasy users had used significantly more cannabis than the female users, and that there was a trend towards them using more ecstasy may have contributed to this finding.

Gender differences in the effects of ecstasy use have also been found using neuroimaging techniques. Reneman et al. (2001a) used SPECT to investigate [^{123}I]β-CIT labelled-serotonin transporter density in moderate (<50 tablets), heavy (>50 tablets) and ex-ecstasy users (who had not used for at least 1 year) and cannabis using controls. They found that heavy female ecstasy users had lower overall serotonin transporter density than both moderate ecstasy users and controls, whereas no significant differences were seen in men. Buchert et al. (2004) found that while both male and female current ecstasy users had reduced serotonin transporter density in several areas (see Chapter 3), the reduction was more pronounced in women.

1.11 Is there evidence for recovery in the human literature?

Pre-clinical literature suggests axonal 'sprouting' following MDMA-induced neurotoxicity: axonal markers of serotonergic neurons have been found to regenerate after MDMA injury (e.g. Scanzello et al., 1993). However, Hatzidimitriou et al. (1999) found abnormal reinnervation patterns 7 years after MDMA-induced axonal injury in primates. While some brain areas showed total recovery and some partial recovery, others had higher levels of axonal markers than observed in controls animals suggesting hyperinnervation. Ricaurte et al. (2000) describe this as a 'pruning' effect on 5-HT axons following MDMA administration, and assert that it is similar to that observed after lesioning: in order to maintain

axonal quantity, loss of nerve terminals in one region is compensated for by increases in others.

It has been argued that the cognitive deficits observed in ecstasy users could reflect long-lasting or even permanent changes in the serotonergic system caused by the neurotoxicity of MDMA. Few studies have investigated ecstasy users who have been abstinent for a long period of time, and those that have, have yielded mixed results.

Morgan (1999) found that although all ecstasy using participants were impaired on immediate and delayed prose recall, those that had not taken the drug for at least 6 months performed better than those that had been abstinent of between one and six months. This was interpreted as tentative evidence for recovery of memory performance. However, Bhattachary & Powell (2001) who found that after initial recovery in the 15 days after ecstasy use (reflecting residual effects of the drug), length of abstinence did not predict performance on prose recall. This implies a more long-lasting deficit. This conclusion is supported by Wareing et al. (2000; 2005), who found that central executive functioning and visuo-spatial working memory were significantly impaired in both current and ex-ecstasy users compared to controls. In this study the ex-users had been abstinent for at least 6 months (with an average abstinence period of 2 years).

Morgan et al. (2002b) attempted to specifically address the question of the presence of recovery of memory after prolonged abstinence from ecstasy. Current ecstasy users, poly-drug users and controls with no history of drug use were compared to former ecstasy users who had been abstinent for at least 6 months (average 2 years). No differences were found between the groups in tests of executive function. Both ecstasy using groups performed significantly worse than controls on immediate and delayed prose recall, and although the result was not quite significant, ex-users performed worse than current users on these tests. This finding is supported by Thomasius et al. (2003) who found that ex-users showed impaired performance compared to drug-naïve controls on both immediate and delayed prose recall, as well as on several trials of the AVLT, whereas no impairment was found in current users.

Gerra et al. (2000b) found a significant reduction of BDHI direct aggressivenss when comparing MDMA users at 3 weeks and 12 months after cessation. Curran & Verheyden (2003) also found that hostility scores on the Aggression Questionnaire correlated negatively with time since last ecstasy use, indicating that aggression diminishes with increased abstinence. Gerra et al. (2000b) also administered the same participants a serotonergic challenge using d-fenfluramine at both time points (see section 1.8.3(ii)). At 3 weeks ecstasy users showed blunted PRL and CORT response to the challenge compared to controls. However, after 12 months CORT response was restored. The authors argue that this may reflect the initial stages of recovery following MDMA-induced serotonergic dysfunction. This idea is supported by Thomasius et al. (2003) who used [^{11}C]McN5652 PET to measure serotonin transporter density in current and ex-ecstasy users in comparison to poly-drug and drug-naïve controls. The results showed that only the current user group showed reduced 5-HT transporter availability. The authors claim that this also provides evidence for the recovery of the serotonergic system which appeared to be independent of cognitive recovery (see above). Buchert et al. (2004) also found no significant differences in serotonin transporter density between ex-ecstasy users, poly-drug controls and drug-naïve controls while current users had reduced densities in several brain areas (see Chapter 3).

However, the idea of serotonergic recovery is not supported by results from a study using tryptophan depletion and augmentation to measure serotonergic function. Curran & Verheyden (2003) administered either a tryptophan-free (T-) or tryptophan augmented (T+) amino acid drink in order to indirectly manipulate 5-HT function in current ecstasy users, ex-ecstasy users (who had not taken the drug for at least 1 year, the average abstinence period being 2.4 years), and a control group matched for premorbid IQ and alcohol and cannabis use. Cognitive tests were administered before and after the amino acid drink. Prior to the drink, ex-users performed worse than both other groups on a test of sustained attention and working memory (Rapid Visual Information Processing), and showed a trend towards poorer performance on both immediate and delayed prose recall. After the T(+) drink, total plasma tryptophan levels in ex-users increased to almost 12 times their baseline level, much higher than the eight-fold increased observed in both current

users and controls. A similar pattern was observed for free plasma tryptophan. The ex-users were the only group to show differences in cognitive performance between T(+) and T(-) conditions. The authors suggest that these findings could reflect alterations in tryptophan metabolism in ex-users, which could in turn relate to serotonergic changes caused by MDMA use, although they admit that if this were the case it would be expected that current users to exhibit the same pattern. They also suggest the possibilities of pre-existing differences in serotonergic function that may make individuals more susceptible to MDMA induced problems, which could in turn prompt the cessation of ecstasy use. This highlights a problem of all studies using ex-users to investigate long-term effects of MDMA. Verheyden et al. (2003b) found that the reasons given by ex-users for stopping using the drug fell into two general categories; lifestyle changes (such as stopping clubbing etc) or reasons related to mental health problems (depression, anxiety etc.). When studying ex-users it is essential to establish the motivation for giving up the drug, as this could be a major confound in studies investigating MDMA-related problems in ex-users. People who give up using ecstasy due to mental health problems could have pre-existing differences in serotonergic function that make them more susceptible to the negative effects of the drug. Fox et al. (2001a) found no difference in cognitive impairment between ecstasy users who reported experiencing ecstasy-related problems and those who felt they had experienced no problems from their use of the drug, implying that experiencing problems attributed to ecstasy use does not relate to any difference in cognitive profile. However, as this group were all still using ecstasy it could be concluded that the problems they report experiencing are not of a sufficient magnitude to prompt them to stop using the drug all together, unlike the ex-user groups discussed above.

To date only one study has used a longitudinal design to investigate the effects of ecstasy uses after cessation. After an initial test session where 60 ecstasy users were found to be impaired on several tests of cognitive function when compared to 30 controls (Gouzouliz-Mayfrank et al., 2003), Gouzouliz-Mayfrank et al. (2005) re-tested 38 of the ecstasy users 18 months later. 17 of these had abstained from ecstasy use between the 2 test sessions while 21 had continued use of the drug. Although they found no evidence of improvement in those participants who had stopped taking ecstasy, indicating no recovery in cognitive function following

abstinence, they also found no evidence of worsening performance in continuing ecstasy users. In fact, performance on one sub-test was improved in the participants who had continued ecstasy use. This surprising result contradicts the findings of another longitudinal study carried out by Zakzanis & Young (2001b) who found increased deficits in performance in ecstasy users over time. Although the results found by Gouzouliz-Mayfrank et al. (2005) could be interpreted as evidence against the idea of MDMA-induced neurotoxicity being responsible for observed cognitive deficits, it is important to remember that the control group was not followed up in this study making the results more difficult to interpret. In addition, of the 22 participants who dropped out of the study after the first test session, 18 were in the heavy ecstasy using group. The failure to follow up these users could bias the results. The lack of evidence for improvement after cessation of ecstasy use could also be questionable as 11 of the 17 ecstasy users who had been abstinent from ecstasy still regularly used cannabis, and in fact 9 tested positive of the day of the second session. The use of cannabis could impair cognition and hide any improvements caused by cessation of ecstasy use. Interestingly, Daumann et al. (2004b) found that continued cannabis use rather than ecstasy was related to severity of psychopathological symptoms in the same participants (see section 1.9).

1.12 Research questions

In this chapter I have reviewed the literature on the acute effects of MDMA in both humans and animals, as well as studies examining the sub-acute and long-term effects of recreational ecstasy use. Pre-clinical data suggesting serotonergic neurotoxicity has unsurprisingly lead to concerns about the effects of ecstasy use in humans, not only in relation to damage to the serotonergic system, but also on processes modulated by 5-HT function including cognitive function and mood, both in the short and the long-term. Thus, this thesis aims to address 2 broad research questions:

What are the long-term effects of ecstasy use?

As outlined in this chapter, impairment in a range of cognitive functions, alterations of mood and changes in serotonergic function have been attributed to the

recreational use of ecstasy. The question of the longevity of these changes after cessation of ecstasy use has been addressed to a lesser extent. Chapters 2 & 3 attempt to investigate the long-term effects of ecstasy use on serotonin transporter density and dopaminergic function in ecstasy users abstinent for at least 1 year. Chapters 4 & 5 aim to investigate cognitive function and aggression in both current and abstinent ecstasy users. These chapters attempt to overcome the confound of poly-drug use in ecstasy users by recruiting a poly-drug control group matched for the use of *all* other recreational drugs.

What are the sub-acute, or mid-week, effects of ecstasy use?

Previous research has found evidence of increased depression and aggression in ecstasy users 3 or 4 days after taking the drug. Chapters 6 & 7 attempt not only to replicate these findings, but also to investigate the possibility of gender differences in these mood effects, and also to further characterise these effects in relation to the suggestion that they are a results of transient serotonin depletion.

Chapter 2: Ecstasy and dopamine

A PET investigation into dopaminergic function in ex-ecstasy users, poly-drug controls and drug-naïve controls

2.1 Introduction

Much of the research into the neurotoxic potential of MDMA has focused on its effects on serotonin (5-HT), but more recently the role of dopamine has also been investigated. Preclinical data has shown that acute MDMA administration induces the rapid release of dopamine, with some areas (e.g. caudate) showing even greater dopamine release than 5-HT release in rats (Gough et al., 1991). The release of dopamine seems to be dependent on 5-HT release: pre-treatment with fluoxetine reduced dopamine release in rats (Koch & Galloway, 1997). There is also some indirect evidence of dopamine release in humans following MDMA administration. Administration of 1.4mg/kg of haloperidol, a D_2 receptor antagonist, reduced participants' subjective reports of positive mood effects following MDMA administration, indicating a role for dopamine in the psychological effects of the drug (Liechti & Vollenweider, 2000). In the short term MDMA administration appears to cause a marked reduction in dopamine. Hansen et al. (2002) found a 35-55% decrease in [H^3]dopamine uptake in rats 1 hour after MDMA administration, although the uptake rate returned to normal after 24 hours. However, despite this type of evidence of the acute and short-term effects of MDMA on dopamine, there seems to be little evidence of long-term consequences.

Although it has been repeatedly demonstrated that MDMA causes neurotoxic damage to 5-HT neurons in rats, it has also consistently been shown that rats seem *resilient* to dopamine neurotoxicity caused by MDMA (for review, see Colado et al., 2004). This resilience has been demonstrated even under conditions that produced high levels of striatal 5-HT loss. For example, Sanchez et al. (2004) administered 'binge' (repeated) doses of MDMA (3 x 4mg/kg) to rats housed in high temperatures (30°C) and found 65% 5-HT loss in the cortex and the hippocampus but no loss of striatal dopamine. Even rats fed on a selenium-free diet

to reduce the antioxidant activity of the brain failed to show dopaminergic damage following MDMA administration (Sanchez et al., 2003). A similar profile has been found in primates: administration of high doses of MDMA leading to 90% reduction of 5-HT in the caudate nucleus had no effect on levels of dopamine (Ricaurte et al., 1988a). Several other studies have found evidence of 5-HT neurotoxicity whist dopamingeric function remains intact (e.g. Colado et al., 1997). To date mice are the only species to show dopamine neurotoxicity following MDMA administration. In complete contrast to its selective 5-HT effect in rats, MDMA is a selective *dopamine* neurotoxin in mice.

Relatively little research has focused on the effect of MDMA on dopamine in humans. Interest in this aspect of the consequences of MDMA use peaked following the startling results from a study by Ricaurte et al. (2002) that claimed to have found evidence of severe loss of dopaminergic axonal markers in both squirrel monkeys and baboons. Huge media interest was sparked as the authors claimed that the dose regime matched that often reported by recreational ecstasy users and therefore indicated that these users were at increased risk of developing neuropsychiatric disorders involving dopamine, such as Parkinson's disease. However, the authors retracted their paper shortly afterwards (Ricaurte et al., 2003) after discovering that, due to a labelling error, the animals had been mistakenly administered methamphetamine rather than MDMA. By this time, concern about the effects of MDMA on dopamine in humans were also being raised following 3 case studies reporting early on-set Parkinson's disease in men who had used ecstasy (Kuniyoshi & Jankovic, 2003; Mintzer et al., 1999; O'Suilleabhain & Giller, 2003), and evidence suggesting that ecstasy users report experiencing involuntary twitches (Parrott et al., 2003). This clearly had huge implications for the millions of recreational ecstasy users across the world. However, given the anecdotal nature of case reports and the lack of reliable information about the subjects' drug use histories, their generalisation to the overall population of ecstasy users has little validity. As argued by Kish (2003), the most likely explanation is that the appearance of Parkinson's in these MDMA users is coincidental. However, interest in the effects of MDMA on dopamine has increased and several studies have now attempted to investigate this in humans.

McCann et al. (1994) investigated serotonergic and dopaminergic function in MDMA users and controls by comparing cerebrospinal fluid (CSF) concentrations of 5-hydroxyindoleacetic acid (5HIAA) and homovanillic acid (HVA), the major metabolites of 5-HT and dopamine (see section 1.8.3(i) for details). They found that while female participants who reported high levels of ecstasy use showed lower levels of CSF HVA than female control subjects, male ecstasy users were no different to male controls.

Gerra et al. (2002) investigated dopaminergic function in ecstasy users by administering bromocriptine, a dopamine agonist. Bromocriptine stimulates growth hormone (GH) and inhibits prolactin (PRL), and these endocrine responses were measured in 12 MDMA users who had been abstinent for 3 weeks and 12 control participants. Gerra et al. (2002) found that although there were no differences in their PRL responses, the increase in GH was significantly lower in ecstasy users than in the controls. As a correlation was found between ecstasy consumption and GH response the authors attribute the blunted GH response to the action of MDMA. However, the MDMA-using participants had all contacted a drugs advice centre and had commenced a drug rehabilitation programme. All had histories of abusing other drugs, including cocaine and heroin. Additionally, four had personality disorders, most showed high levels of novelty seeking behaviours and they scored significantly higher than controls on measures of depression and aggressiveness. On the other hand, the control group had never used psychoactive drugs, did not drink in excess and none had personality disorders. As the authors themselves point out, dopamine is involved in the brain reward system and dopamine release is common to most drugs of abuse, thus it is possible that this evidence of dopaminergic dysfunction reflects a pre-existing difference in drug abusers more related to their personality traits and drug-using behaviours than being caused by MDMA use.

This idea is supported by the results of another similar study by the same group (Gerra et al., 2003). The hormonal response to both being in a stressful situation (giving at 10 minute videoed presentation about themselves to 3 people) and a bromocriptine challenge were measured in 15 male ecstasy users who were very similar in profile to those studied in the previous experiment. The results showed

that controls' levels of cortisol and adrenocorticotropic hormone (ACTH) increased more than ecstasy users after the stressful situations and, in accordance with the previous experiment, that ecstasy users' GH response to the bromocriptine challenge was blunted compared to controls. However, in this case no correlation was found with prior ecstasy use. Once again the ecstasy users had significantly higher scores on measures of aggressiveness, depression and novelty seeking, and 10 had axis II personality disorders. Interestingly, hormonal responses to stress and bromocriptine were correlated with scores on measures of aggression and novelty-seeking, adding more weight to the explanation that the differences in hormonal response may be due to pre-existing differences between the groups related to drug use and its associated personality traits and behaviours. The results are also made more difficult to interpret as a placebo control was not used in either study.

Semple et al. (1999) investigated both serotonin and dopamine transporter availability in recreational ecstasy users with single photon emission computed tomography (SPECT) using the [^{123}I]β-CIT ligand (see section 3.1). Although evidence was found for reduced serotonin transporter density, binding to the dopamine transporter was normal.

Clearly, a major problem with investigating dopaminergic function in ecstasy users is that their use of other recreational drugs may be contributing to any effects found. Non-human primates assessed with 6-[^{18}F]fluoro-L-DOPA (^{18}F-dopa, a measure of presynaptic striatal dopamine function) PET following repeated amphetamine administration show a decrease in dopamine synthesis capacity in the striatum persisting for at least 6 months (Melega et al., 1996). Cocaine abusers have been shown to significantly lower striatal dopamine uptake and D_2 receptor availability than controls (Volkow et al., 1996) and methamphetamine abusers were found to have reduced dopamine transporter density compared to controls in the caudate, putamen, nucleus accumbens and prefrontal cortex (McCann et al., 1998; Sekine et al., 2001). Thus, as the concurrent use of other recreational drugs is very common in ecstasy users, it is clear that controlling for the use of these other drugs is essential when investigating the effects of MDMA on dopaminergic function.

Reneman et al. (2002a) attempted to separate out the effects of amphetamine and ecstasy use on striatal dopamine transporter density in humans. They compared 9 participants who reported the use of both ecstasy and amphetamine in the past 3 months with 29 participants who used ecstasy but who reported no amphetamine use and 15 drug-naïve control subjects using [^{123}I]-CIT to image dopamine transporters using SPECT. The ecstasy + amphetamine group had significantly lower binding ratios than the ecstasy alone group but did not differ from the control group. The ecstasy alone group had significantly higher binding ratios that the controls group. At first glance these results seem to indicate that there is no evidence that ecstasy alone damaged the dopamine system, whereas the combined use of ecstasy and amphetamine leads to a reduction in dopamine transporter density. However, the results are somewhat confused by the fact that the ecstasy alone group have *higher* binding ratios than controls. The authors tentatively suggest that this may be related to evidence of increased binding to the dopamine transporter following acute administration of 5-HT reuptake inhibitors (Fujita et al., 1997). However, as the ecstasy users had been drug free for at least 3 weeks this seems unlikely. In addition, the drug use history for the 2 groups of ecstasy users only extends to 1 year prior to screening, and cocaine use is not mentioned.

The present study was designed to investigate dopaminergic function, cognitive function and mood in abstinent ecstasy users. Presynaptic striatal dopaminergic function was assessed with PET using the ^{18}F-dopa ligand in a group of ecstasy users whose use of other recreational drugs at the time of their ecstasy use made them representative of the general ecstasy using population.

Numerous studies have found evidence of impaired cognitive function in ecstasy users (see sections 1.8.5 & 1.8.6). The majority have demonstrated impairments in episodic memory and learning, and some have also found deficits in working memory and executive function. However, the results from these studies are often contradictory as there are many methodological problems inherent in cross-sectional designs used (see section 1.8.2). The common failure to match ecstasy users with the control group in terms of other drug use is of particular importance as recent work indicates that the use of drugs such as cannabis could be important contributing factors to the impairments observed in ecstasy users (see section 1.9).

Although the majority of studies have found evidence of cognitive impairment in ecstasy users, many fail to adequately match ecstasy users with controls in respect to their use of other recreational drugs, as well as other factors such as levels of education and pre-morbid IQ. In addition, when investigating the effects of ecstasy in abstinent ecstasy users the length of abstinence varies considerably, in some studies being as little as 2 weeks (e.g. Zakzanis & Young, 2001a). The present study aimed to carefully match ex-ecstasy users with a poly-drug control group on the use of all recreational drugs. Further, a criterion for entry into the study was that all ex-users had been abstinent from ecstasy for at least 1 year, and this was verified by hair analysis.

Although no tracer directly measures endogenous dopamine synthesis, ^{18}F-dopa is thought to be one of the best in vivo tracers available. Its uptake reflects a range of activities, including ^{18}F-dopa uptake into the dopamine terminals, its conversion to ^{18}F-dopamine by aromatic amino acid decarboxylase (AADC), and the storage in the presynaptic terminals before release (Piccini, 2004). The principle determinant of its uptake in diseases such as Parkinson's appears to be AADC activity. In order to ascertain the effects of ecstasy use, a control group who had never used ecstasy but who were matched for the use of other drugs, especially those known to affect the dopaminergic system (e.g. cocaine and amphetamine) were also assessed, along with a drug-naïve control group. Hair and urine samples were analysed to check self-reported drug use. All participants were also tested on a battery of tests assessing a broad range of cognitive functions and mood.

Given the evidence of decreased dopamine transporter in ecstasy users who also used amphetamine (Reneman et al., 2002a) it could be predicted that the ecstasy using group may show a deficit in dopaminergic function. This could be reflected in decreased ^{18}F-dopa uptake, as evidenced in primates following amphetamine administration (Melega et al., 1996). No study to date has used this ligand to assess dopaminergic function in drug-using humans.

2.2 Method

2.2.1 Design and participants

Volunteers were recruited into three groups and compared using an independent groups design:

(i) Ex-users who used taken ecstasy on a regular basis (at least 25 occasions) but who had not taken it for at least 1 year.

(ii) Poly-drug users who had used a range of other recreational drugs (including cannabis, cocaine and amphetamines) but who had never taken ecstasy

(iii) Drug-naïve controls who had no history of recreational drug use (except alcohol).

Participants were recruited through magazine advertisement and word of mouth. All gave written, informed consent. The study was approved by the institutional ethics committee (see Appendix 1 for letters of ethics approval and information sheets)

Due to the radiation exposure from a PET scan all participants were required to be male and 25 years old or more. Inclusion criteria for all groups were that the participants were male, aged 25-50, not taking prescribed psychotropic medication or receiving psychological treatment, no current or history of drug addiction, not being depressed as determined by the Structured Clinical Interview for DSM-IV (SCID) , have a score of <18 on the Beck Depression Inventory (BDI; Beck, 1978), have a score of <55 on the Spielberger Trait Anxiety Scale (STAI; Spielberger et al., 1970) no serious head injury in the past, not having drank more that 3 units of alcohol in the 24 hours prior to testing and no use of recreational drugs for at least 3 days prior to testing.

2.2.2 Procedure

A screening interview was conducted with all potential participants to establish their past and current levels of recreational drug use. Those who fitted the criteria for one of the 3 experimental groups were sent a copy of the BDI and STAI with detailed instructions. If the limits for the scores on these questionnaires were not exceeded, participants were provided with a detailed information sheet explaining

both the PET and MRI procedures and the psychological testing. The project was also explained verbally, and they were given opportunity to ask questions and to speak to the radiographer if they wished. On the day of the study, participants arrived at the hospital in the morning after a light breakfast. All participants gave urine and hair samples prior to undergoing the PET procedure. After the PET procedure participants were provided with a light lunch during a rest period of approximately one hour. They then completed the psychological test battery that lasted for approximately 2 hours, followed by the MRI scan.

2.2.2(i) Scanning protocols

The PET scans were performed using an ECAT EXACT HR ++ (CTI/Siemens 966) PET scanner, with an axial field of view of 23.4cm. All subjects were given 150mg of carbidopa and 400mg of entacapone 1 hour before the injection of ^{18}F-dopa to block peripheral aromatic amino acid decarboxylase and catechol-*O*-methyl transferase respectively. A transmission scan was performed prior to injection of ^{18}F-dopa to correct for tissue attenuation. 111 MBq of ^{18}F-dopa was injected intravenously over 30 seconds, and the dynamic emission data was acquired as 26 time-frames over 95 minutes.

2.2.2 (ii) PET data analysis

Parametric images of specific ^{18}F-dopa uptake (Ki maps) were created using a standard multiple-time graphical approach (Patlak & Blasberg, 1985) with an occipital reference input function. The Ki maps were then normalized to an in-house ^{18}F-dopa template created from normal subjects in standard stereotaxic (MNI) space using statistical parametric mapping (SPM99) software. A standard region-of-interest object map that outlined putamen, heads of caudate nucleus and ventral striatum was defined on the ^{18}F-dopa template with magnetic resonance imaging guidance (Whone et al., 2003). This object map was then applied to each normalized parametric Ki map to measure individual caudate and putamen Ki. For each subject, the left- and right-sided Ki values were averaged. Between group differences in striatal Ki were calculated using ANOVA with appropriate post-hoc multiple-comparison correction. The occipital cortext was used as the references region as it shows no specific uptake of ^{18}F-dopa.

2.2.3 Psychological test battery

2.2.3(i) Cognitive function

Immediate and delayed prose recall: (Rivermead Behavioural Memory Tests, (Wilson et al., 1985) episodic memory was assessed by playing a taped passage of prose to the participants. They were required to write down as much as they could recall immediately after presentation and 30 minutes later.

The Buschke Selective Reminding Task: (Buschke & Fuld, 1974): was used to provide indices of verbal learning and forgetting over trials. A list of 16 words was read aloud at a rate of 1/second to the participant who was required to repeat the list back to the experimenter. The participant was then reminded of the words they failed to recall and they attempted to recall the entire list again. This continued for 3 trials. After a 30-minute delay the participant is asked to recall the list again. The outcome measures were memory span (immediate recall after trial 1), learning (number of words recalled on trial 3 – number of words recalled on trial 1), delayed recall (number of words recalled after 30 minutes) and forgetting (number of words recalled in trial 3 – number of words recalled after 30 minutes).

Go/No-go task (Figure 2.1): This task tapped response inhibition. The task consisted of two blocks: a practice block of 30 stimuli and one block of 100 stimuli. Stimuli were eight characters of the alphabet (C, J, H, V, L, N, Q). For the practice block participants were instructed to respond, by pressing a designated key on the computer keyboard as quickly as possible, to each letter on the screen. Each letter appeared for 500ms followed by an inter-stimulus interval (ISI) of 500ms. In the main test block participants were instructed to respond by the same designated key press to all but two (C & N) of the eight letters. These two letters constituted the 'No-go' trials. The proportion of 'Go' stimuli was 75% and of 'No-go' stimuli was 25%. Scores were recorded in terms of hits, commission (response inhibition errors) and reaction times.

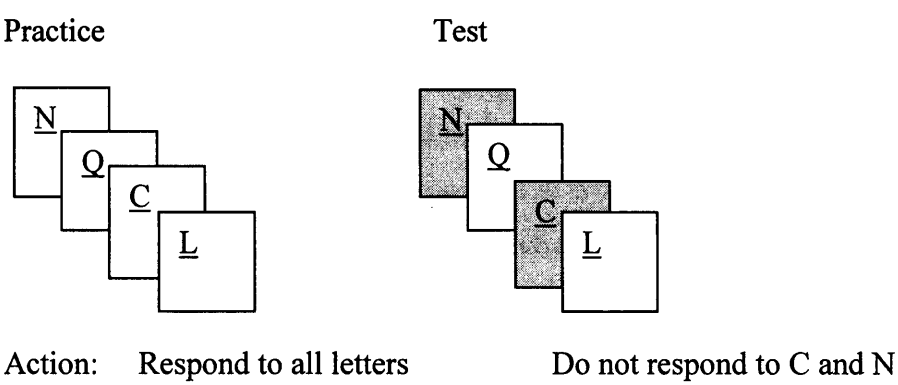


Figure 2.1: Schematic of the Go/No-go task

Rapid Visual Information Processing (Wesnes & Warburton, 1983): used to evaluate sustained attention and working memory. Single digits were presented on a computer screen at a rate of 100 digits per minute for 10 minutes. Participants were required to respond alternatively minute by minute to either 3 consecutive even numbers or 3 consecutive odd numbers. Eight target strings were presented per minute.

The Serial Sevens task was used to tap working memory. A four-digit number was given to the participant who was asked to subtract 7 from this number and continue to count backwards in sevens. The participant did this for 90 seconds and number of correct subtractions and errors were recorded.

Semantic and phonemic verbal fluency: Participants generated as many words as they could in 60 seconds beginning with the same letter (phonetic) or from the same category (semantic). The letter 'S' and the category 'animals' were used.

The Trail Making Test (TMT): a measure of scanning, visuomotor tracking, divided attention and cognitive flexibility. In part A the numbers 1-25 are presented in circles randomly located on an A4 page and participants are required to connect them in ascending order (1–2–3 ...). The participant is instructed to start their trial at the circle marked *Begin* and continue linking numbers until they reach the endpoint (circle marked *End*). In part B participants must alternately switch

between a set of numbers (1–13) and a set of letters (A–L), again linking in ascending order (1–A–2–B …). Participants are asked to complete the trials as fast as possible without making mistakes. Time for completion was used as the primary score for each measure. The time of trial A is taken from the time of trial B to remove the motor speed element and leave a outcome measure related to executive function.

Spatial working memory (Owen et al., 1990) (Figure 2.2): Assesses ability to retain and manipulate spatial information. Participants are required to search through a number of boxes on the screen in order to locate blue tokens, which are 'hidden' inside the boxes. The key instruction is that once a token had been found inside a particular box, that box will not be used again to hide another token in the sequence. There were 4 test trials for each level of difficulty (2, 3, 4, 6 and 8 boxes). Errors are calculated by the number of times a participant returns to a box after looking in it on trials with 4 or more boxes. A strategy score is calculated by counting the number times a participant starts a new search at the same box. A high score indicates a poor strategy.

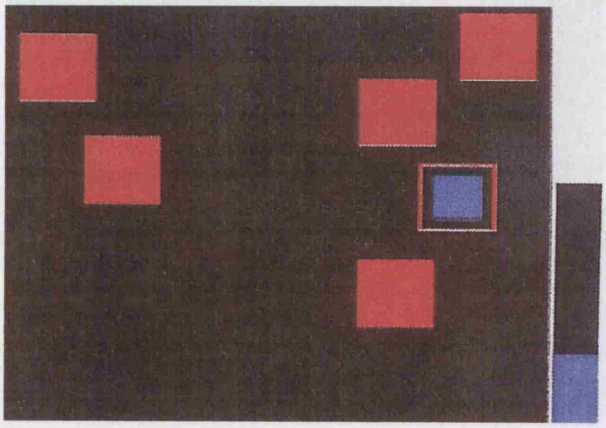


Figure 2.2: Spatial working memory task – 6 box trial

Stockings of Cambridge (Owen et al., 1995) (Figure 2.3): A measure of planning and executive function. Participants see two arrangements of coloured balls in pockets on a computer screen, one in the upper and one in the lower half of the screen. Participants were asked to rearrange the set of balls on the bottom half so that their positions matched the arrangement on the top half of the screen. The minimum number of moves the problems could be completed in ranged from 2-5.

There were four 1-move and four 2-move practice trials followed by eight test trials: two 2-move, two 3-move, four 4-move and four 5-move problems. Subjects are encouraged to plan their moves before actually enacting the solution to the problems. Participants also complete a procedure controlling for motor performance. The balls on the upper part of the screen are moved one at a time, repeating the moves made by the participant in the corresponding previous planning phase. The participants are asked to follow the sequence by moving the corresponding ball on the bottom half of the screen ('copy & follow' condition). There are 3 outcome measures: mean initial thinking time (an indicator of the time taken to plan the problem solution), mean subsequent thinking time (speed of movement after the initial move has been made) and number of problems solved in minimum number of moves.

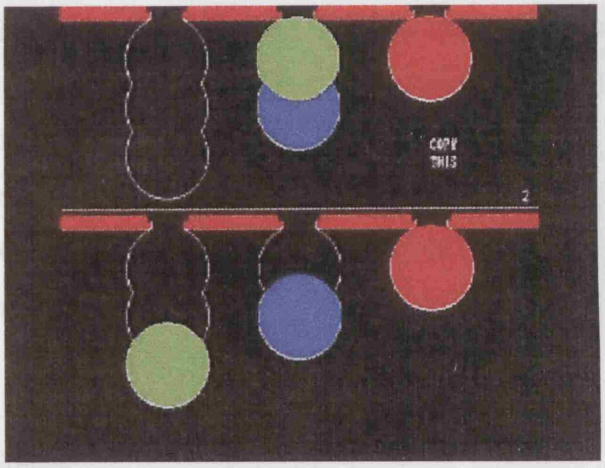


Figure 2.3: Stockings of Cambridge – 2 move problem

Gibson's spiral maze (Gibson, 1977): a test of psychomotor performance requiring had-eye co-ordination. Participants are told to draw round a maze on a piece of paper as quickly as possible without touching the sides. Time taken to complete the maze and errors (number of times the sides were touched) were recorded.

2.2.3(ii) Mood assessments

Impulsivity was assessed using the Barratt Impulsiveness Scale (BS; Barratt & Patton, 1983). This yields 3 subscales: non-planning, motor impulsivity and cognitive impulsivity. Aggression was indexed using the Aggression Questionnaire (AQ; Buss & Perry, 1992) which has 5 sub-scales: verbal aggression, physical

aggression, anger, hostility and guilt. An interpretative bias task designed to assess aggressive cognitive bias, described in detail in section 5.2.2(i), was also administered. In addition, ex-users took part in a short semi-structured interview about their reasons for stopping taking ecstasy.

2.2.3(iii) Drug use history

A semi-structured interview was carried out on all participants to ascertain their levels of drug use, including alcohol. For each substance participants were asked if they had ever taken it, if they had ever used it regularly and if they used it regularly at present. If they had taken it they were asked when the last time they had used it was, how many years they had used it regularly for, how may days in a typical month they used it and how much they used in a typical session. A lifetime estimate of occasions used was obtained by multiplying the number of days used per month by 12, and then multiplying this by the number of years they has used it regularly for. All participants were then also asked what level of education they had attained (either attended school up to the age of 16, up to GCSEs, up to A levels or to university level) and their employment status (unemployed, part-time, full-time, student or self-employed).

2.3 Statistical analysis

Statistical analysis was performed with SPSS version 11. The majority of group differences were tested for significance with one-way analyses of variance (ANOVA). The prose recall task was analysed using repeated measure ANOVA with group as the between-subjects variable and time (immediate or delayed) as the within-subjects variable. The interpretative bias task was also analysed using repeated measures ANOVA with group as the between-subjects variable and sentence type (aggressive or neutral) as the within-subjects variable. Where data violated the assumptions of normality, Kruskal-Wallis tests were used. Post hoc comparisons were performed with Sheffé tests (chosen throughout this thesis as they are conservative and thus account for multiple comparisons). In the case of variables compared using Kruskal-Wallis tests, individual Mann-Whitney U comparisons were carried out (in these cases the α level has been Bonferroni corrected for multiple comparisons). Chi-squared tests were used to compare level

of education and employment status, as well as the number of people reporting having ever tried and those currently regularly using recreational drugs. Pearson's correlations were used to explore the relationship between dopaminergic function, drug use and cognitive performance. Due to the number of correlations performed an alpha level of 0.01 was adopted to minimise the probability of type I errors.

2.4 Results

2.4.1 Demographics

In total 46 male participants aged 25-50 were tested: 17 ex-ecstasy users, 16 poly-drug controls and 13 drug-naïve controls. However, the following participants were excluded: 3 ex-users (2 due to testing positive for cocaine in their urine screens and one for reporting the use of ecstasy 4 months prior to testing), 2 poly-drug controls (one due to scan failure and one due to testing positive for MDMA in the hair screen) and 1 control (tested positive for MDMA in hair screen). Thus, the final data set consisted of 14 ex-users, 14 poly-drug controls and 12 control participants. Data for 2 participants (1 ex-user and 1 control) on the RVIP, Go/ No Go, SWM, SOC and Interpretative Bias task were lost due to computer failure. There were no group differences in age, pre-morbid IQ (Spot The Word), depression (BDI), anxiety (STAI), aggression (AQ) or impulsivity (BS) (Table 2.1). In addition, there were no significant differences between the groups in level of education attained or current employment status. The majority of participants in all groups were in full time employment and had a university degree.

	Ex-ecstasy users	Poly-drug controls	Drug-naïve controls
Age (yrs)	31.07 (5.62)	30.58 (8.15)	30.73 (6.86)
Spot The Word	51.79 (3.09)	49.79 (4.49)	50.67 (3.98)
BDI	8.07 (6.08)	7.71 (4.29)	5.42 (6.36)
STAI	38.93 (10.64)	37.50 (6.73)	36.25 (8.47)
AQ	72.79 (21.24)	74.36 (13.80)	72.25 (17.75)
BS	53.50 (13.27)	55.29 (17.53)	52.25 (16.13)

Table 2.1: Group means (SD) for age, pre-morbid IQ (Spot The Word), depression (BDI), anxiety (STAI), aggression (AQ) ands impulsivity (BS).

The 3 groups were generally well matched for alcohol use (Table 2.2), although a significant group difference was found in the age of first use (χ^2=12.78, df = 2, p=0.002). Post hoc Mann Whitney U comparisons revealed that poly-drug controls (U=9.00, p=0.001) started drinking alcohol younger than controls[1]. The number of participants in each group who currently drank alcohol regularly or currently smoked cigarettes was not significantly different.

There were no significant differences between the ex-users and the poly-drug controls in to the use of cannabis, amphetamines, cocaine, and LSD (Table 2.3). Two poly-drug users had tried ketamine compared to 7 ex-ecstasy users. However, within this 7 only 2 had used it regularly: one had last used 2.5 years ago and one 9 years ago. A small number of participants in both groups had tried magic mushrooms, crack cocaine and heroin very infrequently in the past. Urine screens showed 2 poly-drug users and 1 ex-ecstasy users were positive for cannabis, and the hair analyses revealed 2 poly-drug users and 1 ex-user were positive for cocaine. Hair screens supported the participants' self-reported drug use data.

[1] Due to the group difference in age of first use of alcohol this variable was used as a covariate. This did not significantly affect any of the results and no significant interactions emerged with alcohol. Thus, these results are not reported.

	Ex-ecstasy users (EE)	Poly-drug controls (PC)	Drug-naïve controls (C)	Significant comparisons
Alcohol age of first use (years)	14.821 (3.29)	13.68 (0.95)	16.46 (1.59)	EE vs. C PC vs. C
Alcohol time since last use (days)	16.57 (74.25)	4.29 (3.63)	64.17 (209.71)	-
Alcohol length of regular use (years)	11.43 (6.55)	13.07 (8.55)	11.04 (9.21)	-
Alcohol frequency (days per month)	12.57 (8.71)	10.07 (4.87)	7.63 (6.75)	-
Alcohol dose (units per session)	6.32 (3.71)	8.93 (3.99)	4.54 (3.40)	PC vs. C
Alcohol lifetime occasions	1548.00 (1209.75)	1657.71 (1491.89)	865.00 (599.43)	-

Table 2.2: Mean (SD) alcohol use in ex-ecstasy users, poly-drug controls and drug-naïve controls

	Ex-ecstasy users (EE)	Poly-drug controls (PC)	Significant comparisons
Cannabis age of first use (years)	16.73 (2.06)	15.36 (1.98)	-
Cannabis time since last use (days)	580.62 (909.85)	321.12 (435.84)	-
Cannabis length of regular use (years)	8.58 (5.76)	7.15 (3.27)	-
Cannabis frequency (days per month)	16.28 (12.93)	19.85 (11.70)	-
Cannabis dose (oz. per month)	1.09 (1.37)	1.58 (1.65)	-
Amphetamine age of first use (years)	19.09 (2.12)	18.77 (4.57)	-
Amphetamine time since last use (days)	2659.79 (2188.15)	2538.41 (3205.41)	-
Amphetamine length of regular use (years)	4.17 (2.99)	4.67(5.20)	-
Amphetamine frequency (days per month)	2.77(3.80)	9.50 (8.85)	-
Amphetamine dose (g. per session)	0.83 (0.26)	1.06 (0.58)	-
Cocaine age of first use (years)	22.77 (2.2)	22.15 (6.36)	-
Cocaine time since last use (days)	671.23 (845.28)	493.62 (725.76)	-
Cocaine length of regular use (years)	3.39 (1.80)	5.22 (4.02)	-
Cocaine frequency (days per month)	7.65 (9.67)	5.61 (9.67)	-
Cocaine dose (g. per session)	1.09 (1.04)	1.12 (0.88)	-
LSD age of first use (years)	19.80 (3.85)	19.21 (4.93)	-
LSD time since last use (days)	1646.00 (1442.62)	1802.19 (906.94)	-
LSD length of regular use (years)	3.80 (1.30)	3.00 (1.83)	-
LSD frequency (days per month)	3.60 (3.66)	6.50 (5.00)	-
LSD dose (trips per session)	1.30 (0.67)	1.13 (0.63)	-

Table 2.3: Means (SD) for cannabis, amphetamine, cocaine and LSD use in ex-ecstasy users and poly-drug controls.

The ex-ecstasy users had last used the drug an average of 3.22 (2.77) years ago. They had used on an average of 292.5 (241.47) occasions in their lifetimes. Other data about their levels of use are presented in Table 2.4.

	Mean (SD)	Min	Max
Time since last use (years)	3.22 (2.77)	1	10.5
Age of first use	20.57 (3.46)	16	29
Years of regular use	4.38 (2.88)	1	12
Frequency of use (days per month)	5.75 (3.37)	1	12
Number of tablets used in a typical session	2.32 (0.91)	0.5	4
Lifetime occasions	292.50 (241.47)	48	720

Table 2.4: Mean (SD) of previous ecstasy use in ex-users

2.4.2 Dopaminergic function

A significant group difference was found in dopamine uptake (Ki) in the putamen [$F(2,39)=4.108$, $p=0.024$) (Figure 2.4). Post hoc analysis revealed that the ex-ecstasy users showed a higher dopamine uptake than the control group ($p=0.025$). There were no group differences in Ki value in the caudate or ventral striatum (Figures 2.5a & 2.5b). Voxel-based analysis using statistical parametric mapping (SPM) also showed significantly increased ^{18}F-dopa uptake in the putamen of the ex-ecstasy users compared to the drug-naïve controls ($p<0.05$ corrected for multiple comparison) (Figure 2.6).

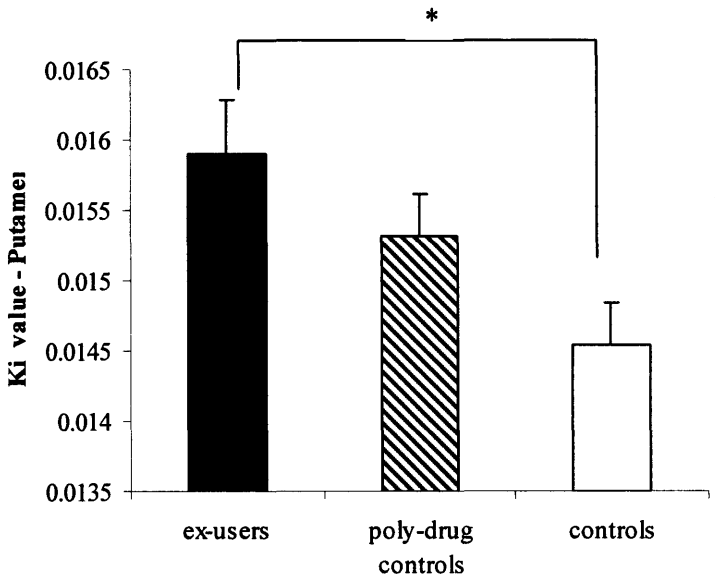
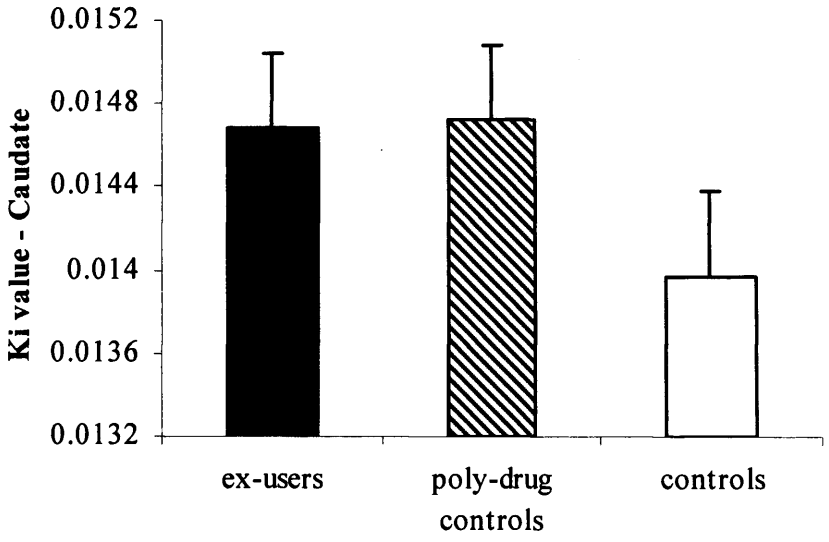
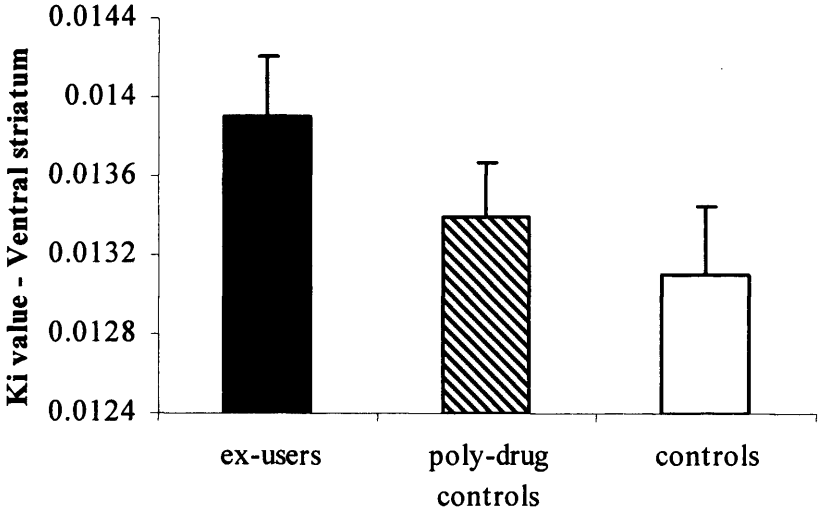


Figure 2.4: Mean (SE) ^{18}F-dopa uptake in the putamen of ex-ecstasy users, poly-drug controls and drug-naïve controls



(a)



(b)

Figure 2.5: Mean (SE) ^{18}F-dopa uptake in the (a) caudate and (b) ventral striatum of ex-ecstasy users, poly-drug controls and drug-naïve controls

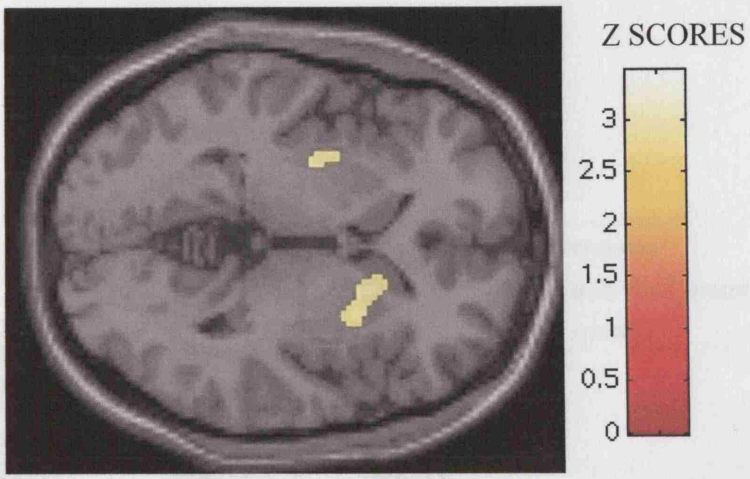


Figure 2.6 SPM image showing the increase in ^{18}F-dopa uptake in the putamen in ex-ecstasy users compared to drug-naïve controls

2.4.3 Cognitive function

Buschke Selective Reminding Task (BSRT)

A significant group difference was observed on the first trial of the BSRT [F(2,39)=5.85, p=0.006] (Figure 2.7). Post hoc tests revealed that both the ex-ecstasy users (p=0.04) and poly-drug users (p=0.01) recalled fewer words than controls. In addition, a main effect of group was observed when looking at learning across the first 3 trials of the task [F(1,37)=3.73, p=0.03) (Figure 2.8). There was no trial x group interaction. There were no significant differences in forgetting (trial 3-delayed recall) or delayed recall after 30 minutes.

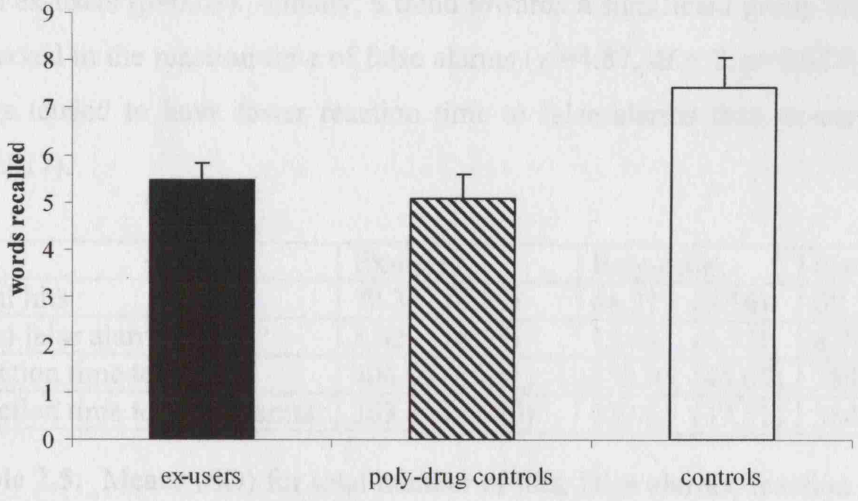


Figure 2.7: Mean (SE) number of words correctly recalled on trial 1 of the BSRT

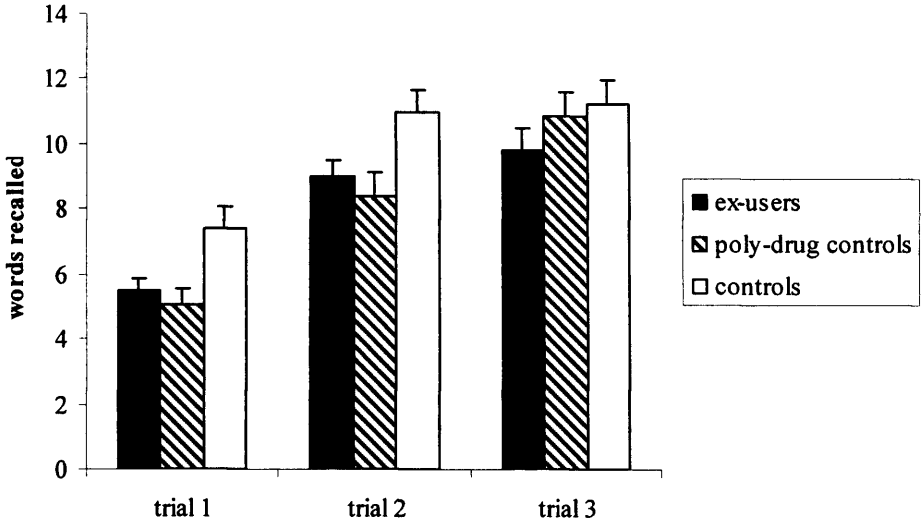


Figure 2.8: Mean (SE) number of words recalled across trials 1-3 of the BSRT

Go/No-go task (Table 2.5)

Analysis of the Go/No go task revealed a significant group difference on the number of hits (χ^2=7.57, df = 2, p=0.023). This reflected the poly-drug users making significantly fewer hits than the ex-users (U=37.5, p=0.008). There was also a trend toward them making fewer hits than the drug-naïve control group (U=45.5, p=0.085). A group difference was also found in number of false alarms ([F(2,37)=6.16, p=0.005]: poly drug users made more false alarms than both ex-users (p=0.01) and controls (p=0.02). A group difference was observed on reaction times to hits [F(2,37)=0.395, p=0.028]. Poly-drug controls reacted faster to hits than ex-users (p=0.03). Finally, a trend towards a significant group difference was observed in the reaction time of false alarms (χ^2=4.87, df = 2, p=0.087). Poly-drug users tended to have faster reaction time to false alarms than ex-users (U=42.0, p=0.017).

	Ex-users	Poly-drug	Controls
Total hits	70.31 (0.84)	66.21 (5.56)	69.36 (2.42)
Total false alarms	8.62 (4.19)	13.64 (4.73)	8.73 (3.47)
Reaction time to hits	404.05 (48.61)	352.95 (45.05)	384.43 (49.85)
Reaction time to false alarms	363.51 (42.49)	320.51 (37.51)	354.27 (68.76)

Table 2.5: Means (SD) for total number of hits, false alarms, reaction time to hits and reaction times to false alarms on the Go/No Go task

Other tasks

No significant group differences were found in immediate & delayed prose recall, the serial 7s task, verbal and category fluency, the Gibson Spiral Maze, RVIP, the TMT or the SWM task (see Appendix 2 for descriptive data). No significant group differences were observed on the interpretative bias task.

2.4.4 Correlations

Ex-users group: The number of days cannabis was used in a typical month correlated negatively with ^{18}F-dopa uptake in the caudate (r=-0.759, p=0.003). There was also a trend for ^{18}F-dopa uptake in the ventral striatum to correlate negatively with the same cannabis variable (r=-0.643, p=0.018). ^{18}F-dopa uptake in the putamen correlated negatively with the total number of false alarms on the go/no go task (r=-0.815, p=0.001) and correlated positively with reaction time to hits (r=0.761, p=0.003). There was also a trend towards a positive correlation between frequency of ecstasy use and reaction time for false alarms on the go/no go task (r=0.667, p=0.013).

Poly-drug control group: ^{18}F-dopa uptake in the putamen correlated negatively with years of regular alcohol use (r=-0.669, p=0.009) and there was a trend toward it also correlating negatively with lifetime occasion of cocaine use (r=-0.642, p=0.013). ^{18}F-dopa uptake in the ventral striatum correlated negatively with amount of cannabis used in a typical month (r=-0.691, p=0.009), years of amphetamine use (r=-0.814, p=0.008), life time occasions of amphetamine use (r=-0.671, p=0.009) and frequency of cocaine use (r=-0.799, p=0.01). There was a trend toward ^{18}F-dopa uptake in the caudate being negatively correlated with years of alcohol use (r=-0.587, p=0.027). Years of cannabis use was negatively correlated with learning on the Buschke task (trial 3 – trial 1) (r=-0.709, p=0.007). Time since last use of cocaine correlated negatively with scores on the BDI (r=-0.693, p=0.009).

Drug-naïve control group: A positive correlation was found between years of alcohol use and BDI scores (r=0.775, p=0.003). There was a trend towards ^{18}F-dopa uptake in the putamen correlating positively with number of units of alcohol consumed in a typical session (r=0.683, p=0.014).

2.5 Discussion

The main finding from the present study is that male ecstasy users who have been abstinent for at least 1 year show increased ^{18}F-dopa uptake in the putamen compared to drug-naïve controls. This could be interpreted as evidence of a long-lasting effect of ecstasy on the dopaminergic system. In some way this result seems counter-intuitive: one might expect ecstasy users to have *reduced* dopamine synthesis. However, if, as Reneman et al. (2002a) tentatively suggest, participants who have used ecstasy and amphetamine have reduced density of dopamine transporters, it is possible that the higher levels of ^{18}F-dopa uptake reflect an upregulation of the dopaminergic system. Although ^{18}F-dopa uptake is reduced in Parkinson's patients, even in the early stages of the illness (Bruck et al., 2005), a recent study by Adams et al. (2005) investigating carriers of a familial form of Parkinson's found evidence of a slight up regulation of AADC while dopamine transporter density was reduced. They suggest that this upregulation of decarboxylase activity could be compensatory in nature, and could maintain dopamine levels and delay the onset of Parkinsonian symptoms. Clearly, as it is impossible for us to comment on dopamine transporter availability in the participants in the current study, the notion of upregulation being responsible for the observed results is purely speculative. In future, it would be interesting to assess dopamine transporter availability as well as ^{18}F-dopa uptake in ecstasy users to try and attain a more comprehensive picture of the operation of the dopaminergic system.

Increased ^{18}F-dopa uptake has also been found in the striatum of unmedicated schizophrenic patients (Hietala et al., 1999; Hietala et al., 1995). In the case of schizophrenia however, there does not appear to be evidence of decreased dopamine transporter density (Lavalaye et al., 2001). The authors suggest that this increase in ^{18}F-dopa uptake reflects increased dopamine synthesis. Nunn et al. (2001) found increased levels of schizotypy on the O-life scale (Mason et al., 1995) in cannabis users compared to non-users and these differences were present in the absence of any differences in depression and anxiety. It would be interesting to see how such a measure was associated to ^{18}F-dopa uptake. Unfortunately, no measure of schizoptypy was administered in the present study. Increased ^{18}F-dopa uptake has

also been found in children with attention deficit hyperactivity disorder (ADHD; Ernst et al., 1999). Interestingly, a recent study by Thomasius et al. (2005) investigated current and ex-ecstasy users, matched poly-drug controls and drug-naïve controls in terms of prevalence of psychopathology. They found that prevalence of ADHD was significantly higher in drug users than in controls, and approached significance when comparing ecstasy users to all controls. Although it is tempting to extrapolate from these findings and suggest and some underlying differences in dopaminergic function that predispose to attention deficit disorders and drug use, it is important to note that this is the only study indicating a relationship between MDMA and ADHD and so caution must be exercised in interpreting the findings. An interesting correlation immerged in the ex-ecstasy users between ^{18}F-dopa uptake in the putamen and performance on the Go/No Go task. It appears that increased uptake is related to better, or less impulsive, performance. It is possible that if increased dopamine up take is a compensatory mechanism, this may also have some effect on performance of response inhibition tasks that are affected by dopaminergic function.

It is possible that pre-existing differences caused the observed differences in dopaminergic function between the groups. Differences in dopaminergic function have been found to predict drug taking patterns in primates. When primates who had previously been individually house were re-housed in groups, levels of D_2 receptors increased in those who became dominant but no change was seen in subordinate monkeys. Interestingly, the subordinate animals self-administered more cocaine (Morgan et al., 2002a). The dopamine system also seems to be in part responsible for how much the effects of the drugs are enjoyed and therefore are reinforcing. Volkow et al. (1999) administered 0.5mg/kg methylphenidate to healthy volunteers and measured their subjective reports of drug liking and D_2 receptor availability using [^{11}C]Raclopride and PET. They found significantly lower D_2 receptor binding in the striatum of participants who reported liking the drugs effects, and that D_2 binding correlated negatively with self-rated scales including happiness and positive mood. Dopamine has also been implicated in the modulation of both personality traits such as novelty seeking and behaviours such as drug taking (Bardo et al., 1996). Drug users often show higher levels of novelty-seeking and impulsivity; it could in fact be these aspects of their personality that

lead them to take drugs in the first instance. Together, these findings indicate the possibility that differences in the dopaminergic system could pre-date or even predict drug use. Although there were no differences in self-rated impulsivity between the groups in the present study, it is possible that this measure is not sensitive enough to pick up subtle group differences, and as the participants in both drug using groups had stopped taking most recreational drugs they may report less impulsive-type behaviours. On the other hand differences in dopaminergic function and/or novelty-seeking do not explain the lack of difference between the poly-drug group and the control group: the poly-drug controls were very well matched to the ex-ecstasy users in terms of the use of almost all other recreational drugs. There is no reason to expect that the predisposition to use ecstasy in particular is different from the use of other stimulant drugs.

Although the poly-drug control group is not significantly different to either the ex-ecstasy user or the control group in respect to ^{18}F-dopa uptake, their Ki values appear to lie in between the two other groups. The higher Ki value in the ex-ecstasy group could reflect an additive effect of using the same amount of other stimulant drugs as the poly-drug controls, and then using ecstasy on top of that. In effect, they have used more stimulant drugs than the poly drug control group, and this may explain the increase in ^{18}F-dopa uptake compared to controls.

Cognitively, there was little difference in performance between the 3 groups. Both drug using groups were impaired on the Buschke Selective Reminding task: they had a shorter immediate memory span and learned fewer words across the initial 3 trials than the control group. Although this may seem surprising due to the broad range of cognitive deficits previously observed in ecstasy users, it is important to note that the groups were extremely well matched in terms of age, pre-morbid IQ, level of education and employment status. There were also no group differences in levels of depression, anxiety, aggression or impulsivity. In addition, the majority of studies investigate current ecstasy users or those abstinent only for a short time (e.g. (Fox et al., 2002; Morgan, 1999). The aim of the present study was to use ex-ecstasy users with a minimum abstinence period of 1 year in order to investigate if cognitive deficits were persistent after this time period. Although some studies have attempted to investigate persistent impairments in ex-ecstasy users there few

have employed as long an abstinence period as the present study (see section 1.11). Curran & Verheyden (2003) was the only other study to have an abstinence period of at least 1 year, and used an almost identical test battery. They found impairments in the ex-ecstasy users on the Buschke task, although in delayed recall rather than learning. Contrary to our findings, they also found that ex-users were impaired compared to controls on the serial 7s tests and on performance on the RVIP task. However, in addition they found that the ex-users were more aggressive and impulsive than the controls. The lack of differences in performance on the cognitive tasks in the present study may reflect a progressive recovery as abstinence time increases. The lack of differences between the groups in terms of mood, depression and anxiety may also account for the differences between these results and other studies. Overall, results from studies of ecstasy users are inconsistent: performance on many of the tests used in the present study has been found to be unimpaired in some studies, while impaired in others (see Tables 1.3, 1.4 & 1.5). Impairments of verbal learning do, however, appear to be one of the more consistent findings across the studies (see Table 1.3), and although our findings support this, it is not possible to attribute the cause of this impairment to ecstasy use as it is also apparent in the poly-drug control group. This is supported by a recent study by Roiser et al. (2005b) who found no significant differences between ecstasy users and controls matched for the use of other drugs on a range of cognitive functions. However, it is important to point out that the numbers of participants in each group are relatively small for comparing performance of cognitive teats. Higher numbers may have revealed more group differences.

A surprising result was the poor performance of the poly-drug users compared to both other groups on the go/no go task. They had fewer hits and made more false alarms, and their reaction times for both hits and false alarms were faster than the other groups, indicating a speed accuracy trade off. This impairment cannot directly be related to response inhibition as they did not only have more false alarms (commissions errors: failure to inhibit the response of reacting to the stimuli), they also had fewer hits. It appears that they were simply going faster and therefore making more mistakes than both other groups. This could reflect increased impulsivity, although no differences were observed on self-rated impulsivity.

Within the ex-ecstasy group, no measure of ^{18}F-dopa uptake correlated with any measure of ecstasy, amphetamine or cocaine use. In the poly-drug using group , however, there were negative correlations between ^{18}F-dopa uptake and various measures of alcohol, cocaine, cannabis and amphetamine use, all indicating that the more these drugs were used the lower the levels of ^{18}F-dopa uptake. In this way the poly-drug users appear to fit what we may expect to be the consequence of the use of these drugs where as the ecstasy using group show no such correlations. It is possible that the use of ecstasy has somehow altered the relationship between drug use and dopaminergic function. However, it is important to note that caution must be exercised in interpreting correlational evidence, especially with small participant numbers and the high number of correlations performed.

In conclusion, the results from the current study highlight the possibility that recreational ecstasy use may cause long-lasting alterations to the dopaminergic system. As this is one of very few studies investigating the effects of MDMA on dopamine, and the first to assess presynaptic dopamine in humans, further research is essential to fully understand the implications of these findings.

Chapter 3: Ecstasy, poly-drug use and serotonin transporters

A PET investigation of serotonin transporter density in ex-ecstasy users, poly-drug controls and drug-naïve controls

3.1 Introduction

Evidence of MDMA-induced 5-HT neurotoxicity from pre-clinical research (see section 1.6) has lead researchers to speculate that humans who take the drug recreationally could be at risk of long-term serotonergic damage. Attempts have been made to investigate serotonergic function in recreational ecstasy users with methods such as serotonergic challenges (e.g. fenfluramine administration), measurements of 5-HT metabolites in cerebrospinal fluid, and recently with more direct neuroimaging techniques (1.8.3 section & Table 1.2).

As one of the consistent changes found in animal brains following MDMA administration is a reduction of serotonin transporter (SERT) density (Ricaurte et al., 2000), attempts have been made to investigate SERT density in human ecstasy users. McCann et al. (1998) used PET to investigate differences in SERT density between 14 abstinent ecstasy users and 15 controls using carbon-11-labelled McN-5652 ([11^C]McN-5652), a radioligand that putatively selectively labels the 5-HT transporter. The results showed that although there were no significant group differences in individually specified brain areas, there were significant global decreases in [^{11}C]McN-5652 binding in the MDMA users, suggesting these participants had reduced density of 5-HT transporter sites compared to controls. They also reported a weak but positive correlation between decreases in transporter binding and amount of previous ecstasy use. However, the validity of this correlation is questionable as it was only evident when control subjects were included in the analysis. Thomasius et al. (2003) used the same ligand to investigate SERT density in 30 current and 31 ex-MDMA users in comparison to 29

poly-drug controls and 30 controls with no history of recreational drug use. In contrast to the results found by McCann et al. (1998), no differences were found between ex-users and controls. However, current users of the drug were found to have reduced distribution volume ratios of SERT availability in the mesencephalon and caudate nucleus. This apparent discrepancy in results is, however, probably due to the difference in length of abstinence of 'ex-users'. The minimum abstinence time in McCann et al's (1998) study was 3 weeks, which is the same as the average abstinence in Thomasius et al's (2003) *current* users group. On average, the abstinent users in McCann et al's (1998) study had not used MDMA for 19 weeks, much less than the average of 73 weeks in Thomasius et al's (2003) abstinent user group. Thus, both results indicate a reduction in SERT binding in MDMA users who have been abstinent for a relatively short time. The finding that MDMA users who have been abstinent for approximately 18 months show no evidence of diminished SERT density suggests that MDMA-induced damage to the serotonergic system may be reversible.

This conclusion is supported by another large scale study carried out by Buchert et al. (2004) using [^{11}C]McN-5652 PET to investigate SERT binding in 30 current and 29 former ecstasy users (with a mean abstinence period of almost 1.5 years), 29 poly-drug and 29 drug-naïve controls. They also found reduced SERT binding in current users compared to all other groups in the mesencephalon and caudate, as well as in thalamus, hippocampus, occipital cortex, temporal lobes and posterior cingulate gyrus. There was no significant difference between the former ecstasy users and the 2 control groups, and a positive correlation was found between length of abstinence and SERT availability in all MDMA users, all adding weight to the idea of serotonergic recovery following cessation of ecstasy use. Interestingly, they also found that the reduction in SERT binding was more pronounced in female than in male ecstasy users, a finding supported by both Reneman et al. (2001a) and de Win et al. (2004) using [^{123}I]β-CIT SPECT, both contributing to the body of evidence indicating gender differences in the long-term effects of ecstasy use (see section 1.10)

Semple et al. (1999) employed SPECT to measure 5-HT transporter binding with the [^{123}I]β-CIT ligand. Results showed that 10 male current ecstasy users showed a

reduction of cortical SERT binding, particularly in the primary sensory-motor cortex. The same technique was used by Reneman et al. (2001b) to investigate differences in SERT binding between current MDMA users, ex-users and control subjects. Although no significant differences were observed in individual brain regions, mean cortical binding was lower in current users than in controls, but ex-users did not differ significantly from either group. De Win et al. (2004) also found evidence of reduced over all [^{123}I]β-CIT binding in current ecstasy users, but only those who had used ecstasy over 50 times. They found no evidence of differences between ex-users abstinent for at least 1 year and controls. Although the validity of [^{123}I]β-CIT has been questioned (Heinz & Jones, 2000), Reneman et al. (2001b) respond to this criticism by citing data from studies using non-human primates showing that [^{123}I]β-CIT binds predominately with serotonin transporters (Farde et al., 1994).

Evidence of alterations in serotonergic functioning could have implications for ecstasy users, as 5-HT has been implicated in a wide range of functions including mood and cognitive function (see section 1.5). The majority of published studies investigating cognition in ecstasy users have demonstrated impairments in episodic memory and learning, and some have also found deficits in working memory and executive function (see sections 1.8.5 & 1.8.6). Many researchers have suggested that these observed cognitive impairments are a functional consequence of MDMA-induced 5-HT neurotoxicity. However, the majority of these studies have not employed measures to assess 5-HT function and thus the hypothesised relationship between impaired cognitive function and alterations in the serotonergic system is purely speculative. In addition, many have methodological problems inherent in cross-sectional designs used (see section 1.8.2), including failure to match ecstasy users with the control group in terms of other drug use. In addition, when investigating cognitive impairments in abstinent ecstasy users the length of abstinence varies considerably, in some studies being as little as 2 weeks (e.g. Zakzanis & Young, 2001a). Associations between altered 5-HT function and impairments in cognitive function have been found in ecstasy users following tryptophan depletion (Curran & Verheyden, 2003) and using PET to assess post-synaptic 5-HT$_{2A}$ receptors (Reneman et al., 2000a). Two of the studies investigating SERT density discussed above have also assessed cognitive function.

Reneman et al. (2001b) tested participants on various assessments of verbal memory and found that both current and former ecstasy users performed worse than controls on tests of immediate and delayed recall. They found no association between any measures of MDMA exposure and 5-HT transporter density, but they did find that greater ecstasy use was associated with greater deficits in immediate recall. These results suggest that although recovery from the neurotoxic effects of MDMA over time is a possibility, this recovery does not seem to extend to memory function. Interestingly, Thomasius et al. (2003) found that of the 4 groups studied, *only* the ex-ecstasy users were significantly impaired on verbal recall. They tentatively suggest that deficits may become apparent after a period of abstinence. However, a more plausible possibility is that the observed cognitive impairments could be related to higher levels of psychopathology (as measured by the SCL-90-R) found in the ex-user group compared to all other groups. Similar results were found by Curran & Verheyden (2003) who reported both cognitive impairments and higher anxiety and aggression in ex-ecstasy users compared to both current users and controls.

Although [^{11}C]McN-5652 has regularly been used to assess SERT densities, Kish (2002) argues that it is not a reliable measure as it has high levels of nonspecific binding, and Parsey et al. (2000) have questioned the reliability of [^{11}C]McN-5652 binding to reflect true SERT binding in brain regions with very low SERT density. In addition, Laruelle et al. (2003) discuss the protracted brain uptake of the ligand as a limitation, as this means the procedure becomes lengthy. An alternative to [^{11}C]McN-5652 is ^{11}C-DASB, a second-generation SERT ligand. A comparison of ^{11}C-DASB with [^{11}C]McN-5652 in baboons (Szabo et al., 2002) found the contrast between brain regions with high and low SERT densities was greater with ^{11}C-DASB. In addition, ^{11}C-DASB was also better at assessing the paroxetine-induced blockade of SERT, and had a faster washout rate. McCann et al. (2005) assessed SERT density in 23 MDMA users abstinent for an average of approximately 5 months (minimum 2 weeks) and 19 controls with PET using both ^{11}C-DASB and [^{11}C]McN-5652. Strong correlations were found between the density of SERT transporters labelled by the 2 ligands not only in the majority of brain regions investigated, but also in individual participants. Both ligands showed global SERT binding was reduced in the MDMA users, and regional differences were also found

in many brain areas including the amygdala, hippocampus, dorsolateral prefrontal cortex and the orbitofrontal cortex. However, the results from the 2 ligands were not entirely in concordance. Whereas a significant positive correlation was found between global SERT binding and length of abstinence using the [^{11}C]McN-5652 compound, this association was not apparent in the data from the ^{11}C-DASB ligand. On the other hand, a weak correlation was observed between SERT binding and typical MDMA dose per month with both ligands.

The present study was designed to investigate SERT density with PET using the ^{11}C-DASB ligand in ex-ecstasy users who have been abstinent for at least 1 year, a poly-drug control group matched for the use of other recreational drugs and a drug-naïve control group. A range of measures assessing cognitive functions and mood were also administered. Given previous research indicating no significant differences in SERT binding in previous ecstasy users abstinent for, on average, over 1 year (Reneman et al., 2001b; Thomasius et al., 2003), I predict that, due to the lengthy abstinence period, no group differences in SERT binding will be observed in the present study. However, given previous studies that find impaired cognitive function in ex-ecstasy users (Curran & Verheyden, 2003; Reneman et al., 2001b; Thomasius et al., 2003), one may expect similar impairments in the present study. On the other hand, this expectation should be balanced by the fact that ex-users in these studies were self-selected populations who had higher levels of emotional disorder. When groups are matched more closely for psychopathology, as in the PET study reported in the previous chapter of this thesis, such group differences in cognitive function may not emerge.

3.2 Method

3.2.1 Design and participants

Volunteers were recruited into three groups compared using an independent groups design:

(i) ex-users who used taken ecstasy on a regular basis (at least 25 occasions) but who had not taken it for at least 1 year.

(ii) Poly-drug users who had used a range of other recreational drugs (including cannabis, cocaine and amphetamines) but who had never taken ecstasy

(iii) Drug-naïve controls who had no history of recreational drug use (except alcohol).

Participants were recruited through magazine advertisement and word of mouth. All gave written, informed consent. The study was approved by the institutional ethics committee (see Appendix 1 for letters of ethics approval and information sheets).

Due to the radiation exposure from a PET scan all participants were required to be 25 years old or more. Inclusion criteria for all groups were that the participants were male, aged 25-50, no history of taking prescribed psychotropic medication or receiving psychological treatment, no history of depression or other psychiatric problems, no current or history of drug addiction, have a score of <18 on the Beck Depression Inventory (BDI; Beck, 1978), have a score of <55 on the Spielberger Trait Anxiety Scale (STAI; Spielberger et al., 1970), no serious head injury in the past, not having drank more that 3 units of alcohol in the 24 hours prior to testing and no use of recreational drugs for at least 3 days prior to testing. The participants who took part in this study also had no history of psychiatric problems including depression according to the SCID or any family history of depression

3.1.2 Procedure

A screening interview was conducted with all potential participants to establish their past and current levels of recreational drug use. Those who fitted the criteria for one of the 3 experimental groups were sent a copy of the BDI and STAI with detailed instructions. If the limits for the scores on these questionnaires were not exceeded, participants were provided with a detailed information sheet explaining both the PET and MRI procedures and the psychological testing. The project was also explained verbally, and they were given opportunity to ask questions and to speak to the radiographer if they wished. On the day of the study, participants arrived at the hospital in the morning after a light breakfast. All participants gave a

urine and a hair sample prior to undergoing the PET procedure. After the PET procedure participants were provided with a light lunch during a rest period of approximately one hour. They then completed the psychological test battery that lasted for approximately 2 hours, followed by the MRI scan.

Detailed descriptions of the cognitive test battery, mood assessments, and drug-use history interview are given in section 2.2.3.

3.2.3 PET scans

Participants had a cannula placed in the radial artery and a venous cannula inserted in the contralateral antecubital vein. The radiotracer [^{11}C]DASB was synthesized as previously described (Wilson et al. 2000) by reaction of [^{11}C]methyliodide with the desmethyl precursor. The standard DASB and the precursor desmethyl DASB were obtained from Target Molecules Ltd., Southampton (UK). [^{11}C]DASB was injected by hand into an antecubital vein as a smooth bolus over 30 seconds. The injected radioactivity dose was approximately 550 MBq. The radiochemical purity of the injected [^{11}C]DASB was high and ranged from 98% to 100 %. All PET scans were performed on the high-sensitivity Siemens/CTI scanner ECAT EXACT3D with an axial field of view of 23.4 cm and 95 reconstructed transaxial image planes (Spinks et al. 2000). To reduce the effect of activity outside the direct field of view in brain scans, the tomograph was equipped with annular side shielding (Spinks et al. 1998). A 5-minute transmission scan using a ^{137}Cs point source was carried out prior to each study for subsequent attenuation correction and scatter correction. The 90-minute 3D dynamic emission scan was acquired in list mode. In the post acquisition frame rebinning, 28 time frames of increasing length were generated (30 s background frame prior to the injection, then 1 15s-frame, 1 5s-frame, 1 10s-frame, 3 30s-frames, 3 60s-frames, 3 120s-frames, 3 180s-frames, 8 300s-frames and 4 450s-frames). The spatial resolution of the images reconstructed using the reprojection algorithm (Kinahan and Rogers, 1989) with the ramp and Colsher filters set to Nyquist frequency is close to isotropic: 5.1 mm full width at half maximum (FWHM) transaxially and 5.9 mm FWHM axially averaged over a radius of 10 cm from the centre of the field of view (Spinks et al., 2000). Arterial whole blood activity was monitored continuously for the first 28 min of the scan with a

Bismuth Germanate coincidence detector (Ranicar et al., 1991). For the initial 10 min during which the peak of radioactivity in the blood occurs and fine temporal sampling of the signal is required, the blood flow rate through the detecter system was set to 5 ml/min. Thereafter the rate of the blood pump was reduced to 2.5 ml/min. Ten discrete arterial blood samples were taken at 3, 9, 15, 21, 28, 35, 42, 50, 70 and 90 min into heparinised syringes. The activity concentration of the whole blood and plasma were measured. Eight plasma samples per scan (at 3, 9, 15, 21, 35, 50, 70 and 90 min) were analysed for metabolites using a semi-automated system with on-line solid-phase extraction (SPE) followed by reverse-phase chromatography with on-line radioactivity and UV detectors and integration system. The plasma samples were loaded onto the SPE column and eluted with di-ammonium hydrogen phosphate (0.01 M) and further analysed using reverse-phase column (μ–Bondapak C_{18} column, 30 cm x 0.78 cm internal diameter) eluted with a mixture of ammonium formate (10 mM) and methanol [35:65 v/v] at a flowrate of 3 ml/min. The eluate was monitored for UV absorbance at 254 nm and radioactivity and subsequent data captured on a PC based integrator. The amount of [^{11}C]DASB and its radioactive metabolites at a given time point was calculated from the decay-corrected integrated radiochromatogram and the levels of radioactivity in the SPE eluate and expressed as a percentage of total plasma sample injected

3.2.3(i) MRI scans and definition of volumes of interest

Regions of interest (ROI) were defined on the co-registered MRI with the help of a probabilistic brain atlas template (Hammers et al., 2003). First, individual MRI image was co-registered with Individual PET image and then each MRI image was segmented and spatially normalized to standard stereological space template image (Montreal Neurological Institute, MNI) using standard software (Statistical Parametric Mapping-2, SPM2; Wellcome Department of Imaging Neuroscience, Institute of Neurology, UCL, London, UK, online at http://www.fil.ion.ucl.ac.uk/spm). The deformation parameters used in the transformation were applied to a probabilistic atlas of brain ROIs, also in standard stereological space (Montreal Neurological Institute, MNI), to provide an individual ROI atlas for each subject. To assist with the ROI measurement, each subject had a magnetic resonance imaging (MRI) scan (GE Signa 1.5 T scanner [GE Medical

Systems, Milwaukee, Wisconsin], spin-echo sequence proton density-weighted image. Regional time-activity curves (TACs) were generated from sampling the grey matter pixels by applying the individual ROI atlas on each [^{11C}]DASB dynamic image using the medical imaging software ANALYZE.

3.2.3(ii) Data analysis

For the generation of the plasma input functions, the time course of the plasma-to-blood ratio, obtained from the first five discrete arterial samples at 3, 9, 15, 21 and 28 min scan time, was first fitted to a sigmoidal. Then the measurement of the arterial whole blood activity obtained from the continuous detector system (Ranicar et al., 1991) was multiplied with that ratio to obtain a total plasma activity curve for the first 28 min of the scan. This curve was then combined with the discrete plasma activity concentration measurements at 35, 42, 50, 70 and 90 min to an input function describing the total plasma activity concentration for the entire scan. Finally, the input function of the activity concentration due to unmetabolised [^{11}C]DASB in plasma was created by multiplying the total plasma activity input function with the function obtained from the fit of the model for the parent fraction in plasma to the eight measurements of the parent compound during the scan. Calculations were performed using Matlab® (The MathWorks, Inc., Natick, MA, USA) on Sun Ultra™ 10 workstations (Sun Microsystems, Inc., Santa Clara, CA, USA). Data analysis was done using Logan plasma input function model. Logan plot is a multiple-time graphical analysis for reversible tracers. It produces volume of distribution (DV) in case arterial plasma is measured and used as model input. Graphical analyses convert the model equations into linear plots, the slopes of which represent measures of tracer binding. The graphical methods are not dependent upon a particular model structure but the slopes can be related to combinations of the model parameters if a model structure is assumed. The input required is uptake data from a region of interest vs time and an input function that can either be plasma measurements or uptake data from a suitable reference region (Logan, 2000).

Regional estimates of total volumes of distribution VD were obtained with Logan analysis (Logan et al., 1990) from 35 min onwards. Regional binding potential (BP) was calculated from total distribution volume (DV) as follows,

$$BP = DV\ (Region) / DV\ (cerebellum) - 1$$

where cerebellar grey matter was used as a reference region. Left and right regions were combined and analyzed as one in order to decrease the chance of a false positive result.

3.3 Statistical analysis

Statistical analysis was performed with SPSS version 11. ^{11C}DASB binding potential was analysed using a repeated measures ANOVA (RMANOVA) with brain area as the within-subjects variable, and group as the between-subjects variable. As Mauchly's test of sphericity was significant a Greenhouse-Geisser correction was used. The majority of other group differences were tested for significance with one-way analyses of variance (ANOVA). The prose recall task was analysed using RMANOVA with group as the between-subjects variable and delay (immediate or delayed) as the within-subjects variable. The interpretative bias task was also analysed using RMANOVA with group as the between-subjects variable and sentence type (aggressive or neutral) as the within-subjects variable. Where data violated the assumptions of normality, Kruskal-Wallis tests were used. Post hoc comparisons were performed with Sheffé tests, or in the case of variables compared using Kruskal-Wallis tests, individual Mann-Whitney U comparisons were carried out (α level Bonferroni corrected for multiple comparisons). Chi-squared tests were used to compare level of education and employment status, as well as the number of people reporting having ever tried and those currently regularly using recreational drugs. Pearson's correlations were used to explore the relationship between ^{11C}DASB binding, drug use and cognitive performance. Due to the number of correlations performed an alpha level of 0.01 was adopted to minimise the probability of type I errors.

3.4 Results

3.4.1 Demographics

In total 42 participants aged 25-47 were tested: 15 ex-ecstasy users, 14 poly-drug controls and 13 drug-nave controls. The following participants were not included in the analysis: 4 ex-users (1 reported using ecstasy 6 months prior to testing, 1 tested positive for MDMA in hair sample, 1 due to failed PET scan following a power cut and 1 due to PET data being corrupted), 5 poly-drug controls (1 requested to leave before the scan was complete, 1 refused MRI, 1 due to failed PET and 2 due to corrupted PET data) and 3 controls (1 tested positive for MDMA in hair sample, 1 due to corrupted PET data and 1 due to unusual MRI results). Thus, the final data set was comprised of 11 ex-ecstasy users, 9 poly-drug controls and 10 drug-naïve controls. Data from the Interpretative bias task was lost for one ex-user due to computer failure.

There were no significant group differences in age, depression (BDI), anxiety (STAI) or premorbid IQ (see Table 3.1). Group differences were found in impulsivity (BS) [$F(2,28)=3.64$, $p=0.041$] and aggression (AQ) [$F(2,28)=6.93$, $p=0.004$] (Table 3.1). Poly-drug controls were more impulsive than controls ($p=0.045$), while both ex-users ($p=0.039$) and poly-drug controls ($p=0.006$) rated themselves as more aggressive than controls.

	Ex-ecstasy users (EE)	Poly-drug controls (PD)	Drug-naïve controls (C)	Significant comparisons
Age	27.91 (3.05)	32.75 (8.96)	34.00 (5.58)	-
Spot the Word	50.09 (4.21)	50.50 (4.11)	51.70 (2.71)	-
BDI	6.73 (4.96)	5.38 (5.58)	3.20 (3.36)	-
STAI	35.82 (9.14)	35.75 (9.85)	31.50 (9.24)	-
BS	51.27 (11.77)	56.50 (11.06)	41.60 (12.96)	PD > C
AQ	69.45 (13.82)	76.00 (17.57)	53.07 (7.56)	PD > C EE > C

Table 3.1: Group means (SD) for age, premorbid IQ (Spot the Word), depression (BDI), anxiety (STAI), impulsivity (BS) and aggression (AQ)

Generally, the groups were well matched in terms of alcohol use, although there was a difference in units of alcohol used per session [$F(2,27)=17.17$, $p=0.001$] (Table 3.2). Poly-drug controls drank more units per session than controls ($p=0.001$). There were no group differences observed in any variable of use for cannabis, cocaine, amphetamines and LSD (see Table 3.3). Two ex-users and 1 poly-drug control had tried benzodiazepines between 1 month and 1 year previously. Three ex-users had tried ketamine between 1.5-4 years prior to testing, and 3 ex-users had also tried heroin between 4-10 years previously. Four controls had tried cannabis 1-3 times, all over 9 years previously.

	Ex-ecstasy users (EE)	Poly-drug controls (PC)	Drug-naïve controls (DC)	Significant comparisons
Alcohol age of first use (years)	14.73 (1.85)	16.00 (1.66)	16.25 (2.49)	-
Alcohol time since last use (days)	4.91 (5.63)	2.67 (2.12)	4.13 (4.29)	-
Alcohol length of regular use (years)	10.59 (2.80)	15.50 (9.07)	13.81 (7.79)	-
Alcohol frequency (days per month)	9.27 (5.83)	9.72 (6.11)	5.75 (3.94)	-
Alcohol dose (units per session)	7.36 (2.50)	9.44 (4.30)	3.00 (1.79)	PC > C

Table 3.2: Mean (SD) alcohol use of ex-ecstasy users, poly-drug controls and drug-naïve controls

	Ex-ecstasy users (EE)	Poly-drug controls (PC)	Significant comparisons
Cannabis age of first use (years)	16.20 (1.87)	18.50 (3.59)	-
Cannabis time since last use (days)	273.65 (462.76)	332.50 (652.65)	-
Cannabis length of regular use (years)	8.43 (3.15)	11.44 (10.10)	-
Cannabis frequency (days per month)	17.75 (11.37)	13.63 (11.17)	-
Cannabis dose (oz. per month)	1.65 (1.61)	0.64 (0.85)	-
Amphetamine age of first use (years)	18.83 (2.62)	20.63 (5.78)	-
Amphetamine time since last use (years)	6.71 (4.85)	4.97 (4.41)	-
Amphetamine length of regular use (years)	1.67 (0.82)	4.63 (7.17)	-
Amphetamine frequency (days per month)	5.17 (7.33)	7.56 (8.93)	-
Amphetamine dose (g. per session)	1.30 (1.93)	1.49 (1.68)	-
Cocaine age of first use (years)	20.75 (1.78)	22.83 (4.36)	-
Cocaine time since last use (days)	749.08 (249.69)	130.17 (152.61)	-
Cocaine length of regular use (years)	3.60 (1.95)	4.75 (3.00)	-
Cocaine frequency (days per month)	5.47 (8.18)	3.50 (4.20)	-
Cocaine dose (g. per session)	2.35 (2.79)	0.67 (0.49)	-
LSD age of first use (years)	17.00 (1.73)	19.67 (3.51)	-
LSD time since last use (years)	5.50 (4.30)	8.00 (4.12)	-
LSD length of regular use (years)	2.25 (1.44)	3.50 (2.12)	-
LSD frequency (days per month)	5.12 (4.33)	1.50 (0.71)	-
LSD dose (trips per session)	2.00 (1.08)	1.00 (0.00)	-

Table 3.3: Mean (SD) cannabis, amphetamine, cocaine and LSD use reported by ex-ecstasy users and poly-drug controls

The ex-ecstasy users had last used the drug an average of 2.85 years ago. They had used it on an average of approximately 187 occasions in their lifetimes. Other variables relating to ecstasy use are presented in Table 3.4.

Results for the urine screens of 11 participants (1 ex-users, 2 poly-drug controls and 6 controls) could not be used due to sample labelling errors. Two ex-users and 1 poly-drug user tested positive for cannabis in their urine. Hair samples supported self-reported drug use.

	Mean (SD)	Min	Max
Time since last use (years)	2.85 (1.47)	1	5
Age of first use	18.00 (2.00)	14	22
Years of regular use	4.18 (2.88)	1.5	10
Frequency of use (days per month)	4.09 (2.25)	1	8
Number of tablets used in a typical session	2.73 (2.02)	1	8
Lifetime occasions	187.36 (154.00)	60	576

Table 3.4: Mean (SD) of previous ecstasy use in ex-ecstasy users

3.4.2 Serotonin transporter binding

A trend towards a main effect of group was found [$F(1,27)=2.88$, $p=0.073$] Post hoc tests revealed a trend towards the poly-drug controls showing lower ^{11C}DASB binding than drug-naïve controls. There was no main effect of brain area or group x brain area interaction.

3.4.3 Cognitive function

A significant group difference was observed in number of hits on the Go/No go task [$F(2,28)=3.63$, $p=0.041$]. Post hoc tests revealed than poly-drug controls scored fewer hits than ex-ecstasy users ($p=0.041$). There were no significant group differences observed on any other test of cognitive function (see Appendix 3 for descriptive data).

3.4.4 Further analysis

One ex-ecstasy user and 2 poly-drug controls reported using cocaine in the week prior to testing. In order to ensure this recent drug use was not affecting the PET

results these participants were excluded form the analysis. The observed trend towards a group differences between poly-drug controls and current users no longer approached significance ($p>0.1$)

As group differences were observed in self-reported impulsivity, aggression and units of alcohol consumed in a typical session, the data was reanalysed using these factors as covariates. The observed group difference in hits on the Go/No Go task was no longer significant after covarying for units of alcohol consumed in a typical session. No other results were significantly affected and no interactions emerged. Thus, these results are not reported.

3.4.5 Correlations

Ex-users: There were trends towards time since last use of ecstasy correlating with ^{11C}DASB binding in the amygdala. Frequency of ecstasy use correlated negatively with ^{11C}DASB binding in the orbitofrontal region ($r=-0.75$, $p=0.008$), posterior cingulate ($r=-0.75$, $p=0.008$) and insula ($r=-0.79$, $p=0.004$).

Poly-drug controls: there was a negative correlation between years of cocaine use and binding in the globus pallidus ($r=-0.91$, $p=0.01$).

3.5 Discussion

The main finding of this study is that ex-ecstasy users abstinent for a minimum of 1 year show no differences in serotonin transporter binding compared to drug-naïve controls. On the other hand, poly-drug controls tended to have lower ^{11C}DASB binding across the regions examined compared to drug-naïve controls.

That no differences were found between the ex-ecstasy users and the controls could be interpreted as evidence of recovery of serotonergic function following abstinence from ecstasy use, and supports previous findings indicating recovery following cessation (Buchert et al., 2004; de Win et al., 2004; Reneman et al., 2001b; Thomasius et al., 2003). The observed correlation between time since ecstasy was last used and ^{11C}DASB binding in the amygdala also supports the idea of recovery

following abstinence. In addition, correlations between frequency of ecstasy use and binding in several regions also support the conclusions of Hatzidimitriou et al. (1999) who suggest that recovery of 5-HT axonal markers is in part dependent on the severity of the original MDMA-induced injury. However, in light of the small number of participants in the present study caution must be exercised when interpreting correlational evidence.

It is possible that poly-drug controls have slightly reduced 5-HT transporter binding as a result of the use of other recreational drugs, and this seems particularly likely as the observed trend towards a reduction in ^{11C}DASB binding was no longer significant when the 3 participants that had used cocaine in the week prior to testing were removed from the analysis. Acutely, cocaine has a high affinity for 5-HT transporters (see Filip et al., 2005, for review), and there is some evidence to indicate that 5-HT transporter binding is reduced in cocaine abusers (Patkar et al., 2004). The observed tendency towards a correlation between cocaine use and binding in globus palladium supports the idea that cocaine use may also affect serotonin transporters.

These findings highlight the importance of matching for poly-drug use, particularly recent cocaine use, when investigating 5-HT function in ecstasy users. It is possible that a part of the reductions observed in current ecstasy users in previous studies may be attributable to the use of cocaine. In addition, the absence of differences between poly-drug controls and drug-naïve controls in the presence of differences between ecstasy users and drug-naïve controls in previous findings may reflect the failure to recruit a poly-drug group match well for the use of *all* other drugs, not just cannabis use.

Thomasius et al. (2006) recently followed up a series of both current and ex-ecstasy users twice at 9-12 month intervals after original testing which assessed 5-HT transporter binding with PET. The ex-users showed no significant differences in 5-HT transporter binding compared to control participants at any of the test sessions. Further, they found no changes in binding in ex-users over time. In addition, *current* ecstasy users showed slight increase in SERT binding over time, despite the fact they had continued to use ecstasy, albeit in reduced quantities. These results

offer an intriguing insight into the process of recovery following MDMA use. They appear to indicate that SERT densities can recover even following a slight reduction of MDMA intake. An interesting aspect of both the present results and of previous research indicating recovery of SERT densities in abstinent ecstasy users is their discrepancy with the pre-clinical research. Hatzidimitriou et al. (1999) investigated SERT densities in primates 7 years after MDMA administration and found that many areas still showed reductions while others had become hyperinnervated and showed greater levels of 5-HT axonal markers than control animals. Fischer et al. (1995) found similar results, and also found that the altered reinnervation patterns were more pronounced in primates than in rats. The discrepancy between the pre-clinical and the human could be explained by several factors. It is possible that the dose regimen of 5mg/kg twice daily for 4 consecutive days subcutaneously has higher neurotoxicity potential than the doses used recreationally by the ex-user in the present study. Thus, different reinnervation patterns would be expected as Hatzidimitriou et al. (1999) suggest that patterns of reinnervation are in part related to the severity of the original 5-HT injury following MDMA administration. Although the authors claim that inter-species scaling indicates that these doses could lie in the range of recreational doses, a recent study found no changes in serotonergic function in rhesus monkeys that self-administered MDMA (Fantegrossi et al., 2004). They did so at a rate of 2-4mg/kg 3 times per week. It could be argued that this is much more comparable to how recreational ecstasy users 'self-administer' the drug. Alternatively, the results of Thomasius et al.'s (2006) longitudinal study could indicate a greater resilience to MDMA-induced serotonergic injury in humans compared to primates.

Overall, little difference was observed in cognitive performance between the groups. Poly-drug users showed some evidence of poor performance on the Go/No go task, although this cannot be attributed to impaired response inhibition as the group difference lay in number of hits as opposed to false alarms. The difference was no longer significant after covarying for units of alcohol used. As discussed previously, the results of studies into the cognitive effects of ecstasy use are equivocal (see section 1.8.5 & 1.8.6). That the ex-users show no differences from controls could indicate recovery following cessation of ecstasy use. However, as no current ecstasy users were tested, and the number of participants in the present

study is low compared to the number of tests administered, firm conclusions cannot be drawn.

In summary, this study replicates previous research indicating no differences in serotonin transporter density in ex-ecstasy users compared to drug-naïve controls. In addition, it suggests that cocaine use may be a confound when investigating 5-HT function in ecstasy users, and thus must be carefully taken into consideration in future research.

Chapter 4: Ecstasy, poly-drug use and cognitive function

An investigation of cognitive function in current ecstasy users, ex-ecstasy users, poly-drug controls and drug-naïve controls

4.1 Introduction

Pre-clinical data indicating serotonergic neurotoxicity following MDMA administration (see section 1.6), and evidence that 5-HT is involved in the modulation of cognitive function (see section 1.5.4) has lead to research into the effects of MDMA on cognitive function in ecstasy users. Although a wide range of impairments have been found (see section 1.8.5 & 1.8.6), the data is equivocal. Among the more consistent findings appear to be deficits in episodic memory and learning (e.g. prose and word list recall, Table 1.3), although deficits have also been observed in a variety of tests of executive functions (Table 1.4 & 1.5). The methodological problems inherent in the cross-sectional designs used to investigate ecstasy users are likely to be responsible for the conflicting findings of the research (see section 1.8.2). Failure to match for the use of other recreational drugs could be particularly important given recent evidence of cannabis contributing to the cognitive impairments observed in ecstasy users (see section 1.9). However, many studies *only* match for cannabis use, ignoring the potential influence of the wide range of other recreational drugs (e.g. amphetamines, cocaine and LSD) that ecstasy users take.

Due to the evidence of long-term serotonergic depletion found in monkeys (Hatzidimitriou et al., 1999) investigations have also been made into the more long-term effects of ecstasy use in humans by testing abstinent users. Although many investigations into cognitive function in abstinent ecstasy users require only short abstinence periods, those that have used longer ones have found some intriguing results. Thomasius et al. (2003) found evidence of impaired verbal recall in users abstinent for an average of approximately 1.4 years when compared to drug-naïve controls. However, the results could be confounded by the finding that the ex-user

group scored higher on several measures of psychopathology. Curran & Verheyden (2003) found that ex-users abstinent for an average of approximately 2.3 years were impaired on measures of verbal learning and working memory compared to both poly-drug controls *and* current ecstasy users. Once again, the results could have been affected by the finding that the ex-users showed higher levels of trait anxiety than both other groups. Only one study to date has employed a longitudinal design to assess the effects of ecstasy on cognitive function following a period of abstention. Gouzouliz-Mayfrank et al. (2005) re-tested 38 participants from a group of 60 ecstasy users originally tested 18 months previously. Of these, 21 reported abstinence or very sporadic use (1-5 ecstasy tablets) between the 2 test sessions, while the remaining 17 continued use. While they found no evidence of improved cognitive performance in the abstinent participants, they also found no evidence of deterioration in those who continued ecstasy use. However, it is important to note that the control group from the original study were not re-tested, making comparison difficult. In addition, a sampling bias may have confounded the results as many of the participants who could not be re-tested were part of the 'heavy user' group at the original test session.

A recent study by Roiser et al. (2005b) investigated cognitive function in 30 current and 20 ex-ecstasy users (abstinent for at least 1 year) compared with 30 poly-drug controls well matched for the use of other recreational drugs and 30 drug-naïve controls. Interestingly, no significant differences were found between the 3 drug using groups on performance on a variety of tests assessing working memory and impulsive decision making, and only 2 sub-tests revealed group differences compared to controls. However, very few group differences were observed between the drug using groups and the drug-naïve controls. On the other hand, Yip & Lee (2005b) found deficits in ecstasy users on almost all cognitive tests used, even though reported ecstasy use was very low in comparison to the majority of other studies (a total of 16-60 tablets taken over 2-3 months). These results once again demonstrate the equivocal nature of the findings relating to cognitive performance in ecstasy users.

The present study was designed to investigate a broad range of cognitive functions in current ecstasy users and in ex-users abstinent for at least 1 year. In an attempt to

eliminate some of the confounding variables in the cross-sectional design, a poly-drug control group, well matched to both ecstasy using groups in use of all other recreational drugs, was also tested. In addition, a drug-naïve control group matched with other groups in terms of age, pre-morbid IQ, level of education, employment status and self-rated depression and anxiety was also assessed.

4.2 Method

4.2.1 Design and participants

Volunteers were recruited into four groups and compared using an independent groups design:

(i) Current ecstasy users who take the drug at least once a month and have taken it on at least 25 occasions.

(ii) Ex-ecstasy users who used to take the drug on a regular basis (on at least 25 occasions) but who had not taken it for at least 1 year.

(iii) Poly-drug users who had used a range of other recreational drugs (including cannabis, cocaine and amphetamines) but who had never taken ecstasy

(iv) Drug-naïve controls who had no history of recreational drug use (apart from alcohol)

Participants were recruited through magazine advertisement and word of mouth. All gave written, informed consent. The study was approved by the institutional ethics committee (See Appendix 4 for ethics approval and information sheet)

Inclusion criteria for all groups were that the participants were male, aged 25-50, not taking prescribed psychotropic medication or receiving psychological treatment, no current or history of drug addiction, not being depressed on the SCID, have a score of <18 on the Beck Depression Inventory (BDI; Beck, 1978), have a score of <55 on the Spielberger Trait Anxiety Scale (STAI; Spielberger et al., 1970) no serious head injury in the past, not having drank more that 3 units of alcohol in the 24 hours prior to testing and no use of recreational drugs for at least 3 days prior to testing.

4.2.2 Procedure

A screening interview was conducted with all potential participants to establish their past and current levels of recreational drug use. Those who fitted the criteria for one of the 4 experimental groups were sent a copy of the BDI and STAI with detailed instructions. If the limits for the scores on these questionnaires were not exceeded, participants were provided with a detailed information sheet explaining the psychological testing. The project was also explained verbally, and they were given opportunity to ask questions. The test session took approximately 2 hours to complete. The majority of participants in the ex-user, poly-drug and drug-naïve groups also took part in PET procedures (see Chapters 2 & 3). To assess recent and prior drug use, all participants gave a urine sample prior to testing, and participates who took part in the PET procedure also gave a hair sample. Full details of the cognitive tests, mood assessments and drug use history questionnaire are given in section 2.2.3.

4.3 Statistical analysis

Statistical analysis was performed with SPSS version 11. The majority of group differences were tested for significance with one-way analyses of variance (ANOVA). The prose recall task was analysed using repeated measure ANOVA with group as the between-subjects variable and time (immediate or delayed) as the within-subjects variable. Learning across trials in the Buschke Selective Reminding task was also analysed using a repeated measures ANOVA with group as the between subjects variable and trial (1-3) as the within subjects variable. Where data violated the assumptions of normality, Kurskal-Wallis tests were used. Post hoc comparisons were performed with Sheffé tests, or in the case of variables compared using Kruskal-Wallis tests, individual Mann-Whitney U comparisons were carried out (α level Bonferroni corrected for multiple comparisons). Due to group differences in total BIS score and the time since cannabis, cocaine and amphetamines had been used, these variables were included as covariates and any significant changes this produced in results are reported. Chi-squared tests were used to compare level of education and employment status, as well as the number of people reporting having ever tried and those currently regularly using recreational

drugs. Pearson's correlations were used to explore the relationship between dopaminergic function, drug use and cognitive performance. Due to the number of correlations performed, an alpha level of 0.01 was adopted to minimise the probability of type I errors.

4.4 Results

4.4.1 Demographics

In total 117 males aged 25-50 were tested. However, only 109 were included in the final analysis as the following were excluded: 5 ex-users (2 reported using ecstasy 6 months prior to testing, 2 urine screens positive for cocaine, 1 hair sample positive for MDMA), 1 current user (urine screen positive for cocaine), 1 poly-drug control (urine screen positive for benzodiazepines) and 1 control (hair sample positive for MDMA). Thus, the final data set comprised of 28 ex-ecstasy users, 25 current ecstasy users, 29 poly-drug using controls and 27 drug-naïve controls. Data for 2 participants (1 ex-user and 1 control) on the RVIP, Go/No Go, SWM were lost, as well as the data for the SOC for these 2 participants and 1 current user, all due to computer failure.

There were no significant differences between the groups in age, pre-morbid IQ (Spot The Word), self-rated aggression (AQ), depression (BDI) or anxiety (STAI) (Table 4.1). A significant group difference was observed on self-rated impulsivity (BS total score) [$F(3,108)=3.71$, $p=0.014$). Post hoc tests revealed that the current users rated themselves as more impulsive than drug-naïve controls ($p=0.014$). Significant differences were observed on both the cognitive impulsivity [$F(3,108)=4.07$, $p=0.009$) and non-planning subscales ([$F(3,108)=2.72$, $p=0.048$): current users score higher on cognitive impulsivity ($p=0.013$) and there was a trend towards them scoring higher on non-planning ($p=0.068$) than controls. Three ex-users, 2 current users, 5 poly-drug controls and 2 controls had received treatment for depression or anxiety in the past. All groups had reached a similar level of education and had a similar distribution across types of employment status (see Table 4.2).

	Ex-users	Current users	Poly-drug	Controls
Age (years)	29.50 (4.69)	28.64 (4.59)	31.93 (8.41)	32.04 (7.59)
Spot the Word	51.29 (3.73)	49.40 (4.26)	50.14 (4.36)	51.11 (3.53)
BDI	7.57 (5.49)	5.16 (3.40)	6.03 (4.17)	4.96 (5.47)
STAI	37.75 (9.67)	35.52 (7.55)	35.76 (6.93)	33.94 (8.44)
AQ	69.29 (17.17)	64.60 (15.48)	69.79 (15.20)	63.04 (18.03)
BS	53.64 (16.02)	**60.80 (13.58)[a]**	54.34 (14.75)	47.04 (15.44)

[a] significantly higher than controls

Table 4.1: Mean (SD) for age, pre-morbid IQ (Spot the Word), depression (BDI), anxiety (STAI), aggression (AQ) and impulsivity (BS)

Employment	Current users	Ex-users	Poly-drug	Controls
Unemployed	16%	18%	10%	15%
Part time	8%	4%	4%	7%
Full time	56%	39%	62%	56%
Student	4%	21%	10%	15%
Freelance	16%	18%	14%	7%
Education				
Up to16	0%	3.5%	7%	4%
GCSE	8%	3.5%	17%	7%
A Levels	24%	11%	24%	15%
Degree level	68%	82%	52%	74%

Table 4.2: Percentages of participants' current employment status and of different levels of education attained.

4.4.2 Drug and alcohol use (Tables 4.3 & 4.4)

No differences were observed between the groups in terms of the time since alcohol was last used, years of regular use and lifetime occasions of use. However, a significant group difference was found on age of first use [$F(3,107)=5.61$, $p=0.001$]. Current users ($p=0.002$) started drinking at a younger age than controls. There was also a group difference in units of alcohol consumed in a typical session $F(3,107)=8.94$, $p=0.001$]. Both current users ($p=0.001$) and poly-drug controls ($p=0.001$) drank more units of alcohol per session than control participants[2].

[2] Due to the significant group differences in units consumed in a typical session, this variable was used as a covariate. This did not significantly affect any of the results and no significant interactions emerged with alcohol. Thus, these results are not reported.

Alcohol	Ex-ecstasy users (EE)	Current ecstasy (CE)	Poly-drug controls (PC)	Drug-Naïve controls (C)	Significant comparisons
Time since last use (days)	10.50 (33.55)	2.12 (1.56)	3.59 (2.91)	34.19 (142.65)	-
Age of first use	14.66 (2.59)	13.76 (2.83)	14.47 (1.94)	16.33 (1.86)	CE > C
Years of regular use	10.91 (4.94)	9.34 (4.81)	14.43 (9.09)	12.38 (8.48)	
Number of days used in a typical month	10.43 (7.53)	13.28 (7.82)	10.88 (6.17)	7.90 (5.91)	
Amount used in a typical session (units)	6.98 (3.26)	8.84 (4.74)	9.29 (3.56)	4.44 (5.60)	CE > C PC > C

Table 4.3: Mean (SD) for alcohol use variables in ex-ecstasy users, current ecstasy users, poly-drug controls and drug-naïve controls

Of the 3 drug using groups, only 2 ex-users and 1 poly-drug control reported never having used cannabis. The only significant group difference apparent within the measures of cannabis use was length of time since last use ($\chi2$=8.66, df=2, p=0.003). Post hoc Mann Whitney U comparisons revealed that current users had smoked cannabis more recently than both ex-users (U=118.50, p=0.002) and poly-drug controls (U=210.00, p=0.002). Percentages of participants who reported current regular use of cocaine and cannabis are reported in Table 4.4. Ten participants in the control group reported trying cannabis 1-3 times between 2 and 10 years previously. Table 4.5 shows group means (SD) for length of use, frequency of use, usual dose etc. of cannabis, cocaine, amphetamine and LSD use

	Ex-users	Current users	Poly-drug
Cannabis	26%	56%	43%
Cocaine	8%	64%	32%

Table 4.4: Percentage of participants in the drug using groups reporting current regular use of cannabis and cocaine

Time since the last reported use of, cocaine ($\chi2$=16.83, df=2, p=0.001) and LSD ($\chi2$=21.48, df=2, p=0.001) showed group differences. Current users had used cocaine more recently than ex-users (U=118.50, p=0.001), and LSD more recently than both ex-users (U=76.00, p=0.001) and poly-drug controls (U=38.00, p=0.001). Only 2 poly-drug controls and 2 current users reported current regular use of amphetamines (>1 per month). There was no reported current regular use of benzodiazepines, 5 current users reported regular ketamine use and 1 ex-user and 1 current user reported regular LSD use. Participants were excluded if their urine sample tested positive for any drug apart from cannabis. The samples for 2 ex-users, 3 poly-drug controls and 9 controls were lost due to sample contamination or laboratory error. The following percentages of participants in each group tested positive for cannabis: ex-users – 15%, current users – 64%, poly-drug users – 19%, controls – 0%.

	Ex-users	Current users	Poly-drug
Cannabis			
Time since last use (days)	433.56 (719.57)	49.28 (147.08)	309.55 (517.95)
Age of first use	16.65 (1.92)	16.12 (2.86)	16.04 (2.62)
Years of regular use	8.34 (4.72)	9.93 (6.35)	10.37 (9.13)
Number of days used in a typical month	16.70 (11.72)	16.35 (11.37)	17.73 (11.47)
Amount used per month (oz.)	1.45 (1.72)	1.06 (1.16)	1.63 (1.884)
Cocaine			
Time since last use (days)	777.90 (859.31)	27.52 (47.71)[a]	560.08 (917.62)
Age of first use	21.66 (2.41)	20.84 (3.35)	22.52 (5.66)
Years of regular use	3.46 (1.78)	4.01 (3.28)	4.64 (3.48)
Number of days used in a typical month	6.92 (8.90)	3.48 (3.31)	5.03 (7.11)
Amount used in a typical session (grams)	1.74 (1.86)	0.58 (0.38)	0.91 (0.70)
Amphetamine			
Time since last use (days)	2445.62 (1870.72)	842.08 (1241.20)	2142.20 (2605.81)
Age of first use	18.93 (2.17)	18.33 (3.82)	18.54 (3.61)
Years of regular use	2.93 (2.30)	4.33 (5.90)	4.18 (5.63)
Number of days used in a typical month	4.04 (5.43)	3.50 (2.37)	6.85 (7.18)
Amount used in a typical session (grams)	1.25 (1.00)	0.72 (0.43)	0.84 (0.49)
LSD			
Time since last use (days)	1754.05 (1346.61)	522.09 (778.04)[a]	2802.68 (2311.13)
Age of first use	18.60 (3.15)	18.13 (3.72)	19.42 (4.24)
Years of regular use	2.85 (1.65)	5.25 (4.17)	2.94 (1.67)
Number of days used in a typical month	4.25 (3.58)	1.50 (0.58)	3.93 (4.03)
Amount used in a typical session (trips)	1.70 (0.89)	1.60 (0.65)	1.00 (0.46)

[a] significantly less time than ex-ecstasy users and poly-drug controls

Table 4.5: Mean (SD) for cannabis, cocaine, amphetamine and LSD use

	Ex-users	Current users
Time since last use (days)	1017.21 (789.26)	14.20 (9.50)**
Age of first use	19.39 (2.96)	18.20 (3.23)
Years of regular use	4.17 (2.73)	7.28 (4.70)*
Number of days used in a typical month	5.30 (3.17)	2.92 (2.16)**
Amount used in a typical session (tablets)	2.53 (1.44)	3.86 (2.39)*
Lifetime occasions	264.86 (233.98)	288.00 (420.88)
Highest number of tablets in one session	5.41 (3.84)	10.54 (8.39)**

*** p<0.05, **p<0.01**

Table 4.6: Mean (SD) of ecstasy use

Several differences were observed between the ex-users and the current users in terms of patterns of ecstasy use (Table 4.6). As would be expected, the length of time since participants had used ecstasy was significantly longer in the ex-user group ($U=0.00$, $p<0.001$). In addition, ex-users had used ecstasy regularly for significantly fewer years then current users ($U=208.00$, $p=0.001$) and took fewer tablets on average per session ($U=208.500$, $p=0.001$). However, ex-users reported using ecstasy more frequently than current users ($U=173.00$, $p=0.002$). There was a significant difference in the highest number of ecstasy tablets participants reported having used in one session ($U=172.00$, $p=0.002$), whereby current users reported higher numbers of tablets than ex-users. One participant reported having used 40 tablets in one session. The significant group differences remained when this outlier was excluded. There were no significant differences in age of first use or total number of occasions used or total number of tablets used.

4.4.3 Cognitive tests

Buschke Selective Reminding Task: A significant group difference was apparent on trial 1 of the task [$F(3, 108)=6.56$, $p<0.001$]. Post hoc tests indicated that both current users ($p=0.002$) and poly-drug users ($p=0.008$) recalled fewer words than controls (Figure 4.1a). A significant group difference was also found on the delayed trial ($\chi2=11.03$, $df=3$, $p=0.002$). Post hoc tests revealed that current users recalled fewer words than controls ($U=162.50$, $p=0.001$) and that both ex-users ($U=264.00$, $p=0.053$) and poly drug users ($U=286.50$, $p=0.08$) showed a trend toward recalling fewer words than controls (Figure 4.1b). In addition, significant main effects of trial [$F(2, 210)=221.07$, $p<0.001$] and group [$F(1, 105)=7.41$, $p<0.001$] were found on learning across the first 3 trials of the task (Figure 4.1c).

Current users (p=0.001) and poly-drug users (p=0.005) recalled fewer words at each trial than controls, while there was a trend toward ex-users remembering less then controls (p=0.078). There was no group x trial interaction. However, after co-varying for time since last use of cannabis, the observed group differences were no longer present. The same pattern was observed after co-varying for time since last use of amphetamines and cocaine.

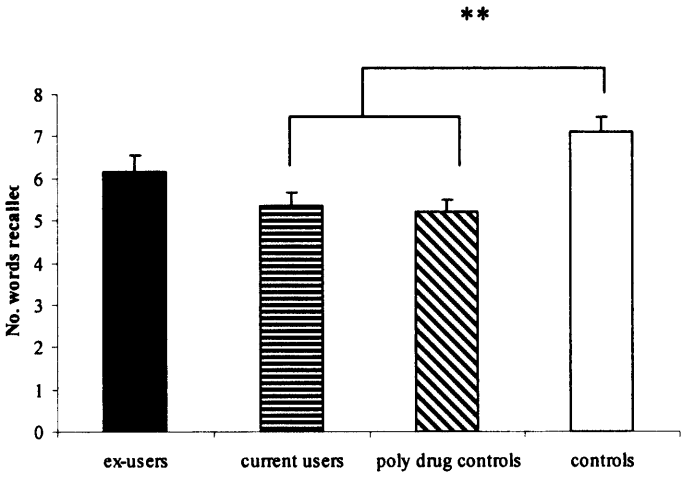


Figure 4.4a: Mean (SE) number of words recalled on BSRT task trial 1

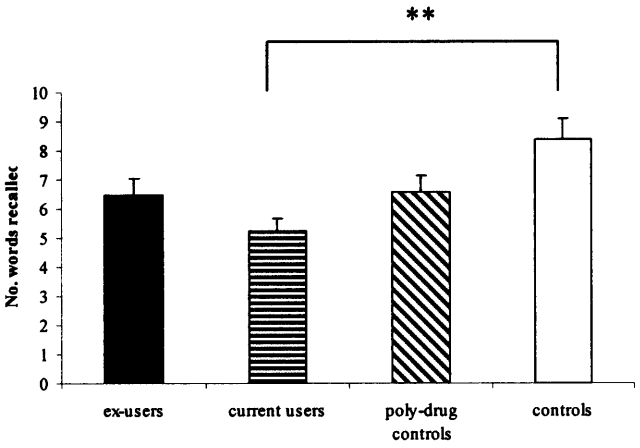


Figure 4.4b: Mean (SE) words recalled on BSRT task delayed trial

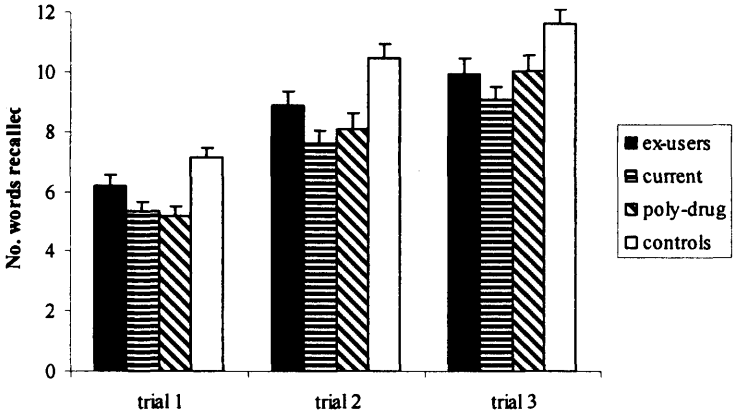


Figure 4.4c: Mean (SE) number of words recalled across trials 1-3 of the BSRT task

Stockings of Cambridge: A significant group difference was found in mean initial thinking time [F(3, 105)=3.41, p=0.02]. Ex-users had longer initial thinking time than current users (p=0.034) (Figure 4.2). There were no group differences in subsequent thinking time or in number of problems solved in the minimum moves. However, after co-varying for BS total score there was no longer a significant group difference.

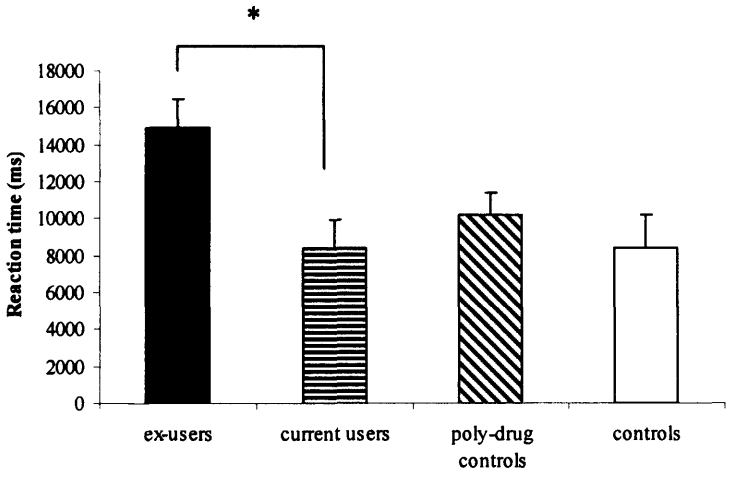


Figure 4.5: Mean (SE) initial thinking time for the SOC task

Go/No go (Figures 4.6a-c): A significant group difference was found in the total number of hits ($\chi 2$=26.37, df=3, p<0.001). Post hoc tests revealed that the current users had fewer hits than both the ex-users (U=97.51, p<0.001) and the controls (U=172.00, p=0.004), and than the poly-drug users also had fewer hits than the ex-

users (U=154.50, p<0.001) and the controls (U=231.00, p=0.013). A significant group difference was also observed in reaction time to hits ($\chi 2$=9.38, df=3, p=0.025). Current users had faster reaction times to hits than both ex-users (U=222.00, p=0.034) and controls (U=184.00, p=0.008). Poly-drug users had faster reaction times than controls (U=258.00, p=0.045) and tended to respond faster than ex-users (U=283.00, p=0.075). A significant difference in false alarms was also found [F(3,106)=4.706, p=0.004]. Poly-drug users had more false alarms than both ex-users (p=0.029) and controls (p=0.015). After co-varying for time since last use of cannabis there was no longer a significant group effect for reaction time to hits. The group differences for total hits and false alarms remained significant.

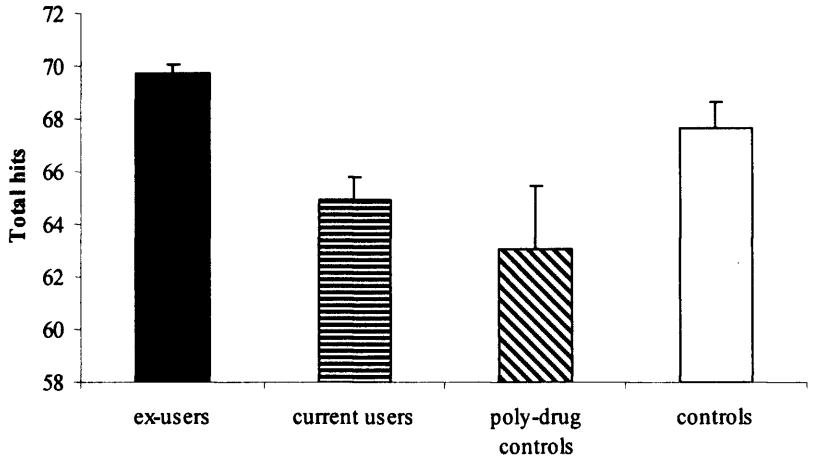


Figure 4.6a: Mean (SE) number of hits on the Go/No go task

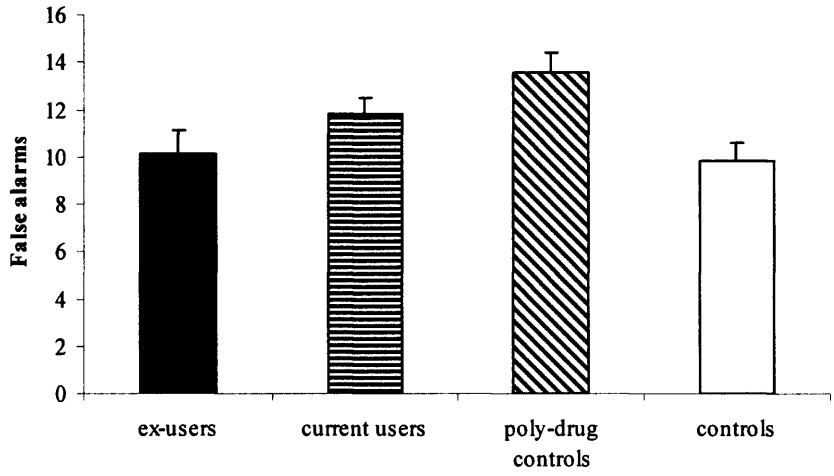


Figure 4.6b: Mean (SE) number of false alarms on the Go /no go task

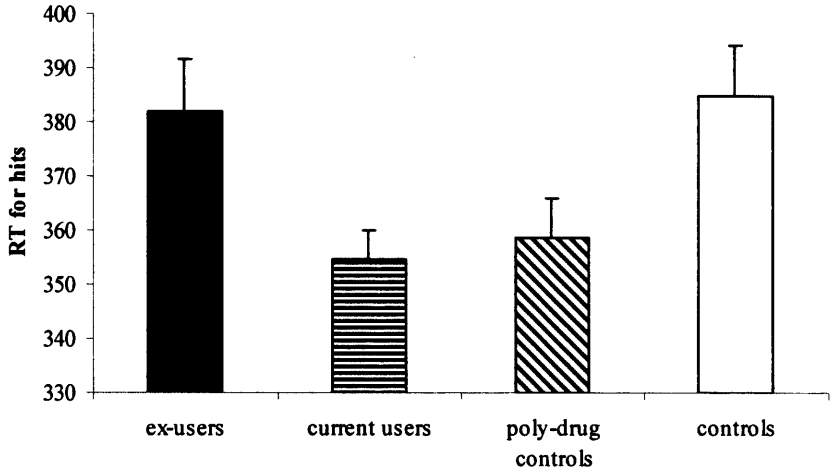


Figure 4.6b: Mean (SE) reaction time to hits on the Go/ no go task

Other tasks

No significant group differences were found in immediate or delayed prose recall, RVIP, serial 7s, verbal fluency, spatial working memory or the trial making test (see Appendix 5 for descriptive data).

4.4.4 Correlations

Ex- users: There was a trend towards mean initial thinking time on the SOC correlating negatively with number of ecstasy tablets used in a typical session (rho=-0.44, p=-0.021) and amount of cannabis used per month (r=0.40, p=0.014). The number of false alarms on the Go/No go task tended to correlate with amount of cannabis used per month (r=0.47, p=0.018) and amount of cocaine used in a typical session (rho=0.64, p=0.014). There were trends toward time since last use of both cocaine (rho=-0.43, p=0.031) and alcohol (rho=-0.41, p=0.038) correlated negatively with the non-planning sub-scale of the BS. Finally, there was a trend toward number of words recalled on the delayed trial of the Buschke task correlating negatively with the motor impulsivity sub-scale of the BS (rho=-0.43, p=0.02).

Current users: There was a trend toward mean initial thinking time correlating negatively with number of ecstasy tablets used per session (rho=-0.45, p=0.021).

False alarms on the Go/No go task correlated with lifetime occasions of amphetamine use (rho=0.50, p=0.008), and tended to correlate with frequency of cannabis use (r=0.47, p=0.014). Frequency of amphetamine use tended to correlate with the non-planning sub-scale of the BS (r=0.68, p=0.031), while frequency of cocaine use tended to correlate with the motor sub-scale of the BS (rho=0.43, p=0.04).

Poly-drug users: Mean initial thinking time on the SOC task correlated with age of first use of alcohol (rho=0.50, p=0.006). Total score on the BS correlated with amount of amphetamines (r=0.64, p=0.002) and tended to correlated with amount of cocaine (rho=0.54, p=0.021) used per session.

Controls: Memory span (Buschke trial 1) tended to correlate negatively with frequency of alcohol use (r=-0.42, p=0.033).

4.4.5 Further investigation of ecstasy using groups

Tables 4.6 & 4.7 show the responses of the ex and current ecstasy users on a range of questions investigating the drugs mixed with ecstasy and the mood effects of ecstasy use.

What drugs do/did you mix with ecstasy?	Ex-users	Current users
Alcohol	82%	92%
Cannabis	79%	72%
Cocaine	46%	96%
Amphetamines	43%	24%
What do/did you use to chill out after using ecstasy?		
Alcohol	54%	48%
Cannabis	86%	72%
Benzodiazepines	7%	8%
Experienced low mood a few days after ecstasy? *% yes*	82%	88%
Do/did you think this was related to ecstasy use? *% yes*	87%	96%
Problems concentrating related to ecstasy use? *% yes*	50%	60%

Table 4.7: Results of questions to ecstasy users regarding their use of the drug

Positive effects	**Ex-users**	**Current users**
Increased	0%	8%
Remained the same	32%	24%
Decreased	68%	68%
Negative effects		
Increased	71%	24%
Remained the same	25%	52%
Decreased	4%	24%
Physical effects		
Increased	21%	16%
Remained the same	64%	52%
Decreased	15%	32%

Table 4.8: Percentage of ex and current ecstasy users reporting increased, decreased or similar levels of the positive, negative and physical effects of ecstasy use over time

The 2 ecstasy-using groups responded similarly for the majority of questions. One-way analyses of variance were carried out to compare performance of cognitive tasks between those participants that reported experiencing problems concentrating that they thought were related to their ecstasy use and those who did not. No significant main effects or interactions were found. One-way analyse of variance were carried out to compared depression (BDI), anxiety (STAI) and aggression (AQ) scores of participants who reported increased or constant/decreased negative effects of taking ecstasy. A significant main effect of group was found for depression ($U=186.00$, $p=0.003$). Those who reported increased negative effects of ecstasy had higher depression scores (Figure 4.7).

No significant differences were observed in depression, anxiety, aggression or cognitive function when comparing heavy (>100 occasions) with light (<100 occasions) across the 2 ecstasy using groups.

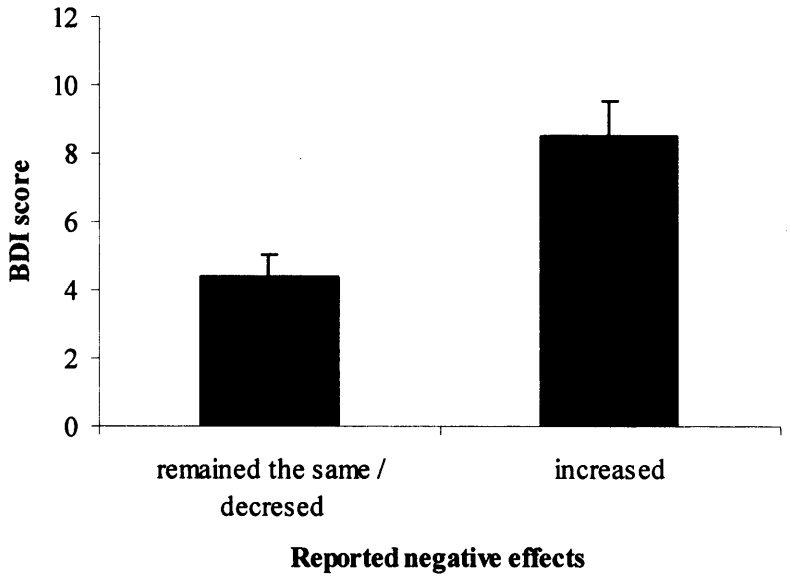


Figure 4.7: Mean (SE) depression scores for ecstasy using participants reporting increased or decreased/constant negative effects of ecstasy

4.5 Discussion

Significant group differences in cognitive function were observed on only 3 of the 11 tasks administered. There was a general tendency towards impaired learning and recall in the 3 drug using groups: compared to drug-naïve controls, current ecstasy users and poly-drug controls had a shorter memory span and learned fewer words across trials on the Buschke Selective Reminding Task, while ex-users tended learn fewer words across trials. Current users also recalled fewer words at the delayed trial, and there was also a similar trend for poly-drug users and ex-users. In addition, current ecstasy users and poly-drug users made fewer hits and had faster reaction times to hits on the Go/No go task than both ex-users and controls, while poly-drug users also had more false alarms than ex-users and controls. Finally, ex-users had a longer initial thinking time on the Stockings of Cambridge task than current users, indicating that they were taking longer to think about the problem before starting to solve it. No significant group differences were observed on immediate and delayed prose recall, Rapid Visual Information Processing task, the

Serial Sevens task, semantic and phonemic verbal fluency, the Trail Making Test, Spatial Working Memory and Gibson's Spiral Maze.

The evidence of impaired learning and recall in the 3 drug using groups is in accordance with the findings of other studies that find both ecstasy users and poly-drug controls have memory impairments compared to drug-naïve controls (see Table 1.3). This finding appears to implicate recreational drug use in general, rather than ecstasy user *per se*, in memory impairment. However, the group difference was no longer significant after covarying for the time since cannabis was last used. This is perhaps not surprising given the evidence that cannabis use leads to memory impairments (see Lundqvist, 2005, for review) and that these deficits have been observed for up to 28 days after abstinence (Solowij et al., 2002). As a much higher percentage of current users tested positive for cannabis in their urine, it is possible that the more significant cognitive deficits observed in the current users was due to residual effects of cannabis use. Pope et al. (2001) found that cognitive deficits following heavy cannabis use appear to be reversible, and the present results appear to support this finding. Covarying for the time since both cocaine and amphetamines were last used also removed the group difference. This highlights the crucial importance of matching groups for the use of all other recreational drugs, not just cannabis. The failure to do this may have lead to many studies implicating ecstasy use in leading to cognitive deficits, whereas the use of other stimulants may also have contributed to the findings. An interesting element to these results is that the current users and the poly-drug controls had a significantly shorter memory span than the controls while the ex-users did not. Although this could be an indication of recovery in the ex-users it is not possible to claim that this is recovery from impairments caused by ecstasy use as deficits are present in drug users who have never taken ecstasy. As the current users and the poly-drug controls report more *current* drug use than the ex-users, it may indicate recovery from deficits caused by drug use in general.

Impaired performance on the Go/No go task is thought reflect deficits in response inhibition. Covarying for the time since cannabis was last used removed the group difference for reaction time to hits, making it unlikely that the reduction in hits found in the current users and poly-drug users was the result of a speed-accuracy

trade off. Although poor response inhibition is often associated with drug use, this deficit appears only in 2 of the 3 drug using groups. However, this discrepancy may be related to the patterns of *current* drug use that distinguish the groups. A higher proportion of current ecstasy users and poly-drugs users report current regular use of both cannabis and cocaine than ex-users, although this failed to reach significance when comparing ex-users and poly-drug users on current cannabis use. The fact that the majority of ex-users no longer take recreational drugs may have lead to a reduction in impulsive behaviours. The observed correlations between cannabis, cocaine and amphetamine use and number of false alarms on the Go/No go task support the idea that drug use in general is related to reduced response inhibition.

The ex-user group took longer than current users to think about problems on the Stockings of Cambridge task before starting to solve them. This could reflect the ex-users needing longer to work out the solution than current users, an interpretation that would fit with previous research finding cognitive deficits in ex-users (Curran & Verheyden, 2003; Thomasius et al., 2003). However, after covarying for impulsivity scores the group difference was no longer significant. Current users had higher BIS scores than ex-users (60.80 ±13.58 *vs.* 53.64 ±16.02), thus an alternative explanation is that the current users are more impulsive than the ex-users so begin the problem quicker. However, the difference on the BS was not significant, and as no other differences were observed in performance on the SOC task, clear conclusions cannot be drawn. Interestingly, correlations between impulsivity scores on the BS and cannabis, cocaine and amphetamine use are apparent in all drug using groups. Although impulsivity has previously been linked to ecstasy use this result supports the alternative explanation that impulsivity is a trait associated with drug use in general (see Section 1.8.9iii).

This study also revealed some interesting results that could reflect the changing pattern of ecstasy use. Although the 2 ecstasy using groups had used ecstasy on a very similar number of occasions (current = 264.86, ex = 288.00), the current users used it for longer and took more tablets per occasions than the ex-users. In addition, our findings mirror recent reports indicating a rise of cocaine use in the

UK (Roe, 2005): only 46% of ex-users took cocaine conjointly with ecstasy compared to 96% of current users.

The results of the present study appear to contradict previous findings suggesting cognitive impairments in ex-ecstasy users (Curran & Verheyden, 2003; Thomasius et al., 2003). However, as discussed previously, the ex-user groups in these studies showed higher levels of psychopathology whereas in the present study all groups were well matched on measures of depression, anxiety and aggression. In addition, the ex-users investigated by Curran & Verheyden (2003) had continued the use of cocaine after cessation of ecstasy (they used almost 3 times as frequently as current users), whereas the majority of the present sample had stopped using cocaine.

Interestingly, there were no significant differences in cognitive function between ecstasy users (both current and ex) who reported experiencing problems concentrating that they believed were related to their ecstasy use and those who did not. A similar result was found by Fox et al. (2001a) (see section 1.11). These findings suggest that ecstasy users' subjective experience of cognitive problems does not match their actual performance on cognitive tasks. This may be due to their preconceptions about the effects of ecstasy use, or it may imply that they are aware of more subtle problems that standard cognitive tests do not reveal. Ecstasy users who felt that the negative effects of taking the drug had increased over the time they had used it had higher depression scores than those that felt they had either remained the same or decreased. Again, this could be interpreted in several ways. It is possible that participants with pre-existing higher levels of depression are more susceptible to the negative effects of ecstasy use. On the other hand, increased depression could be among the negative effects the participants attributed to their ecstasy use. This highlights one of the many problems with cross-sectional designs as the lack of information about participants prior to their drug use means no clear conclusions can be drawn. The fact that a higher proportion of ex-users thought that negative effects had increased (71% vs. 24%) may indicate that these negative effects were part of their reason for stopping ecstasy use.

In light of the large body of research reporting cognitive impairments in both previous and current ecstasy users it may seem surprising that very few group

differences were observed in the present study. However, recent studies that have attempted to minimise confounding variables have also found little evidence of group differences. For example, Roiser et al. (2005b) administered a battery of cognitive tests to 4 groups similar to those in the present study and found only 2 significant group differences: ex-users were impaired compared to drug-naïve controls on one sub-test assessing spatial ability (copying a pattern); and current users were quicker to perform mental rotations than controls. However, the group difference between current users and controls was no longer apparent after controlling for alcohol use and the ex-users scored higher than controls on a measure of impulsivity. Essentially, Roiser et al. (2005b)'s results support the findings of the current study in providing little evidence of cognitive impairment caused by ecstasy use. Overall, the results of research into cognitive effects of ecstasy use are inconsistent (see Tables 1.3, 1.4 & 1.5), the present results appears to be in line with the majority that find no evidence of deficits in executive functions and working memory. In addition, the issue of publication bias must be taken into consideration. Dafters et al. (2004), who also found no evidence of cognitive impairment in ecstasy users, comment that it is likely that "failure to find evidence of MDMA's detrimental effects on cognition is under-reported due to the reluctance of scientific journals to publish non-significant results".

This study highlights the importance of matching groups for as many factors as possible when attempting to explore the effects of ecstasy use. Clearly, matching a control group for the use of other recreational drugs is essential. As mentioned earlier, previous studies claiming to have associated cognitive impairments to ecstasy use rather than poly-drug use often do not match adequately for other drugs (e.g. Rodgers, 2000). This is undoubtedly due to the difficulties in recruiting participants who use similar levels of cannabis, amphetamines and cocaine as ecstasy users but who have never taken ecstasy. This is reflected in the not only in the failure of other studies to match adequately, but also the lack of research investigating the cognitive effects of *recreational* cocaine and amphetamine use: studies to date on these stimulants concentrate virtually exclusively on chronic addiction and withdrawal. While so many studies focus on the cognitive consequences of recreational ecstasy use, why do more not investigate these issues in recreational cocaine and amphetamine users? This lack of information about the

cognitive effects of other stimulant drugs, and the established link between cannabis and memory impairments, have lead to researchers citing cannabis as the most important drug to match for when investigating cognitive function in ecstasy users. The present study highlights the need to match for amphetamine and cocaine use. Matching for pre-morbid IQ is also important: Simon & Mattick (2002) found that IQ was a more significant predictor of memory than cannabis use (see section 1.9). As discussed above, failure to match for mood such as depression, anxiety, aggression and impulsivity could also confound results. Not only are the drug using groups in this study exceptionally well matched in terms of the use of all recreational drugs, but in addition urine samples were taken to verify recent drug use whereas the vast majority of previous studies have relied exclusively on self-reported drug-use information.

Although the present study attempted to overcome some of the methodological problems associated with cross-sectional designs, many of those discussed in section 1.8.2 may still confound the results. An important problem could be that a sampling bias may have lead to the lack of deficits in ex-users. Verheyden et al. (2003b) identified 2 types of reasons for the cessation of ecstasy use: those related to mental health problems (e.g. feeling depressed, feeling anxious) and those related to lifestyle changes (e.g. having children, stopping clubbing). It is conceivable that these 2 groups of ex-users also differ in cognitive ability. Much larger samples of ex-users are needed to investigate this possibility further. It is also possible that the tests administered were not sensitive enough to pick up subtle changes in cognitive function. However, given the number of previous studies that have found deficits on these and similar tests, this does not seem likely.

Although researchers consistently suggest that cognitive deficits could be caused by the consumption of MDMA in ecstasy tablets, the majority do not employ measure of 5-HT function. The basis of this claim is the link between the serotonergic system and cognitive function, but as discussed in section 1.5.4, this link is far from clear. Curran & Verheyden (2003) found a strong correlation between serotonergic function (as measured by levels of plasma free tryptophan following tryptophan augmentation) and delayed recall in ex-users, suggesting a link between alterations of the serotonergic system and cognitive function in ecstasy users. However, the

fact that the majority of pre-clinical studies find changes in serotonergic function in the absence of any functional changes indicates a far more complex relationship than the MDMA-induced neurotoxicity argument proposed by much of the research. Some fascinating new research has suggested that polymorphisms of the 5-HT transporter gene may be associated with ecstasy users' performance on an affective Go/No go task (Roiser et al., 2005a). It is possible that these genetic variations may be associated with individual differences in vulnerability to MDMA-induced changes in the serotonergic system and thus to changes in cognitive function. Although further research is required to investigate this possibility, it could reveal an intriguing explanation, in part at least, for the conflicting results in the ecstasy literature (see Section 5.5).

In conclusion, the present study provides evidence to suggest that recreational drug use, in particular *recent* drug use, may lead to subtle memory impairments, regardless of whether ecstasy has been used or not.

Chapter 5: Ecstasy and Aggression

A investigation of aggressive interpretative bias in current ecstasy users, ex-ecstasy users, poly-drug controls and drug-naïve controls

5.1 Introduction

Serotonin has been implicated in a range of human behaviours including aggression (see section 1.5.2). Although it seems paradoxical that a drug which acutely causes intense feelings of empathy, love and closeness to others could also be responsible for increased aggression, consistent evidence of this effect has been found in ecstasy users 3 or 4 days after taking the drug but not a week after (Curran et al., 2004; Hoshi et al., 2004; Verheyden et al., 2002). Given the evidence of long-term serotonergic depletion following MDMA administration in animals (see section 1.6.3), and more recent evidence indicating changes in serotonergic functioning in human users (see section 1.8.3) concerns have also been raised about the possibility of more long-term increases in levels of aggression in recreational ecstasy users.

In contrast to the consistent sub-acute research, findings relating to the long-term effects of ecstasy use on aggression are equivocal. The majority of studies have used a variety of self-rating measures to assess aggression, anger and hostility and have found no significant differences between ecstasy users and controls (Morgan, 1998; Verkes at al., 2001; McCardle et al., 2004). In one case, *lower* aggression was found in ecstasy users compared to a drug-naïve control group (McCann et al., 1994). Parrot et al (2000), however, found increased hostility on the SCL-90 in a group of heavy ecstasy users (average of 371 occasions). In addition, Gerra et al. (1998; 2000b; 2001; 2002) found that MDMA users showed higher levels of direct aggressiveness (as measured by the Buss-Durkee Hostility Inventory) than controls 3 weeks after last taking ecstasy. However, it is likely that these finding are related to the sample of ecstasy users tested. All 4 studies by Gerra and colleagues have similar samples: the participants had contacted a drug addiction service and had started a long-term psychosocial rehabilitation course. This indicates that they are

not representative of the general ecstasy using population, the majority of whom will never seek help for an ecstasy related drug problem.

Attempts have also been made to assess aggression in abstinent ecstasy users. Gerra et al. (2000b) re-tested participants 12 months after the original test session and, in contrast to the results showing increased aggression 3 weeks after cessation of ecstasy use, no significant group differences were found. On the other hand, Thomasius et al. (2003) found higher self-rated aggression on the SCL-90-R in ecstasy users abstinent for at least 20 weeks compared to drug-naïve controls, although they did not differ significantly from current ecstasy users or a poly-drug control group. In addition, Curran & Verheyden (2003) found that ex-users abstinent for at least 1 year scored significantly higher than both current users and poly-drug controls on the AQ.

Results from the studies above could be confounded due to the demand characteristic associated with self-report measures. Only 2 studies to date have used more objective measures to investigate levels of aggression in ecstasy users. Gerra et al. (2001) used the Point Subtraction Aggression Paradigm (PSAP) to assess levels aggression in 12 male ecstasy users abstinent for 3 weeks. In this task, participants are lead to believe that they can see the responses of another participant on the screen. They are told that both 'players' can earn monetary rewards and subtract money from the other person using button presses. The participants are systematically provoked by having money removed from their total by the fictitious other person. Thus, three types of response were elicited: reward directed responses, in which a monetary reward is earned; aggressive responses, in which money is subtracted from the other person; and escape responses, in which it is not possible to gain rewards but having money subtracted is avoided. Neuroendocrine response to the task was also assessed by measuring plasma levels of noradrenaline and adrenaline. They found that ecstasy users showed significantly more aggressive responding than controls, whereas no significant differences were observed in escape or reward responses. In addition, levels of noradrenaline and adrenaline increased significantly more in ecstasy users than in controls following the task. However, the observed difference in amount of aggressive responses could be due to the sample of ecstasy users tested. As mentioned above, all 12 participants had

started a rehabilitation program. Four fitted the criteria for Axis II personaltity disorders, while another 3 partially fitted the criteria. Seven experienced low mood and dysphoria in the time since they had stopped taking ecstasy and 50% reported relationship conflict with parents. It is possible that the increased aggressive responding observed is more related to such psychological problems, which could well pre-date the onset of ecstasy use. In addition, the control group was made up of hospital staff who, it could be argued, are used to dealing with conflict and, more crucially, not responding in an aggressive manner when provoked. Baseline plasma cortisol was found to be higher in ecstasy users. The authors themselves point out that this could indicate the ecstasy users finding the test procedure more stressful than controls. This possibility is supported by the greater increases in noradrenaline and adrenaline observed in the ecstasy users. This appraisal of the situation could in itself lead to more aggressive responding. Although there is a correlation between aggressive responding and number of ecstasy tablets consumed, the reliability of this association is questionable due to the small number of participants and the unreliability of self-reported drug use data. Finally, as the control group had no history of previous drug use and the ecstasy users had used a range of other recreational drugs, the possibility that history of drug use in general, rather than ecstasy specifically, is associated with increased aggressive responding cannot be ruled out.

Bond et al. (2004) attempted to overcome the confound of poly-drug use in ecstasy users by testing a control group who had used other recreational drugs. In order to investigate the more long-term effects of ecstasy they also tested a group of ex-ecstasy users, abstinent for at least 1 year. Rather than using a task that elicits aggressive behaviour, they measured aggressiveness by looking at cognitive bias towards material with aggressive content in an information processing task based on previous research showing that high trait anger is associated with an attentional bias towards anger related cues (e.g. Van Honk et al., 2001), and that ambiguous stories are more likely to elicit aggressive endings from participants with high trait aggression (e.g. Dill et al., 1997). Short stories concerning a fictional character in an ambiguous situation that could be interpreted as anger provoking were presented to participants. The character reacted in either an angry or a non-angry way, and the time taken to read (process) the sentence that described the reaction was

measured. Participants were also required to make up endings to complete the stories. The 32 participants in each group were randomly allocated to receive an amino acid drink either depleted or augmented with tryptophan. The task was carried out 6 hours after administration of the drink. The results showed that although the ex-users had significantly higher self-rated aggression, all participants were faster to process the angry rather than non-angry sentences. Surprisingly, there was little effect of tryptophan depletion, although there was a trend toward participants in this group producing more aggressive endings to the stories. The finding that all drug users had a cognitive bias toward aggressive material suggests that increased aggression may be a pre-existing trait in people predisposed to drug use, rather than being directly related to, or caused by, ecstasy use. Although no drug-naïve control group was investigated to substantiate this claim, the authors cite unpublished data in which non-drug users showed the opposite pattern: non-angry sentences were processed faster than angry ones.

Copello & Tata (1990) used an information processing approach to investigate aggression in violent and non-violent offenders and non-offending controls. They based their task on Novaco's (1978) cognitive model of anger arousal, which describes the importance of an individual's cognitive appraisal of a situation in mediating their response to it: that aggressive people process aggressive information faster than people who are not aggressive. Coppella & Tata (1990) presented their participants with ambiguous sentences that could be interpreted in a neutral or an aggressive manner (e.g. "the painter drew the knife"). They also included material than could be interpreted as anxiety inducing (e.g. "Mark's speech made everyone giggle"). They measured reaction times to sentence completion and also to recognition of the sentences once the meaning had been made unambiguous, with either an aggressive meaning ("the painter pulled out the knife") or a neutral meaning ("the painter sketched the knife"). The social anxiety questions were made unambiguous to have either threatening meanings (Everyone ridiculed Mark's speech") or non-threatening meanings ("Everyone enjoyed Mark's speech"). Using this task, Copello & Tata found that offenders recognised more sentences that had been given aggressive meanings than non-offender controls. No such pattern was found for the general anxiety responses. Interestingly, no differences were found between violent and non-violent offenders. Increased

aggressive cognitive bias has been found in ecstasy users a few days after taking the drug using an extended version of this task developed by Bond (Curran at al., 2004; Hoshi et al. 2006). The present study aims to assess aggressive cognitive bias in both current and ex-ecstasy users (abstinent for at least 1 year) compared to a control group matched for the use of other recreational drugs and a drug-naïve control group using the same task. As previous findings are conflicting, it is unclear whether higher self-rated aggression will be found in the ecstasy using groups. However, given Bond et al.'s (2004) findings, I hypothesise that aggressive cognitive bias will be found in all the drug using groups. An important additional aim is to assess whether the increase in interpretative bias found using this task by Curran et al. (2004) and in Chapter 6 of this thesis in ecstasy users 4 days after taking the drug is a *transient* effect or a more *chronic* effect still apparent after longer abstinence. This is the first study to include a drug-naïve control group when assessing aggression in ecstasy users using an information processing paradigm.

5.2 Method

5.2.1 Design and participants

Volunteers were recruited into four groups and compared using an independent groups design:

(i) Current ecstasy users who take the drug at least once a month (on at least 25 occasions).

(ii) Ex-ecstasy users who used to take the drug on a regular basis (on at least 25 occasions) but who had not taken it for at least 1 year.

(iii) Poly-drug controls who had used a range of other recreational drugs (including cannabis, cocaine and amphetamines) but who had never taken ecstasy

(iv) Drug-naïve controls who had no history of recreational drug use (except alcohol).

Participants were recruited through magazine advertisement and word of mouth. All gave written, informed consent. The study was approved by the institutional ethics committee (see Appendix 4 for ethics approval and information sheet).

Inclusion criteria for all groups were that the participants were male, aged 25-50, not taking prescribed psychotropic medication or receiving psychological treatment, no current or history of drug addiction, not being depressed on the SCID, have a score of <18 on the Beck Depression Inventory (BDI; Beck, 1978), have a score of <55 on the Spielberger Trait Anxiety Scale (STAI; Spielberger, 1970) no serious head injury in the past, not having drank more that 3 units of alcohol in the 24 hours prior to testing and no use of recreational drugs for at least 3 days prior to testing.

5.2.2 Procedure

A screening interview was conducted with all potential participants to establish their past and current levels of recreational drug use. Those who fitted the criteria for one of the 4 experimental groups were sent a copy of the BDI and STAI with detailed instructions. If the limits for the scores on these questionnaires were not exceeded, participants were provided with a detailed information sheet explaining the psychological testing. The project was also explained verbally, and they were given opportunity to ask questions. The test session took approximately 2 hours to complete, and included a battery of cognitive tests and mood assessments described in detail in section 2.2.3, as well as the interpretative bias outlined below. The participants in the ex-user, poly-drug and drug-naïve groups also took part in PET procedures (see Chapters 2 & 3). All participants gave a urine sample prior to testing, and participants who took part in the PET procedure also gave a hair sample.

5.2.2(i) Interpretative bias task

The task assessing cognitive bias to ambiguous sentences used by Coppella & Tata (1990) and extended by Bond et al. (unpublished data) was administered to participants. The stimuli consisted of 36 unambiguous neutral sentences interspersed with 24 ambiguous sentences, which could be interpreted as either aggressive or neutral (e.g. "The painter drew the knife"). For the recognition task, 72 sentences were prepared, 48 of which were presented to any given subject. For the ambiguous sentences, 24 disambiguated versions were presented: 12 consistent with an aggressive interpretation (e.g. "The painter pulled out the knife") and 12 consistent with a neutral interpretation (e.g. "The painter sketched the knife"). The

remaining 24 sentences consisted of 12 neutral sentences with the same meanings (but slightly different wording) to those presented previously, and 12 new unambiguous neutral sentences (Figure 5.1). Half of the participants in each group were presented with one set of disambiguated sentences and the other half the opposite set. The neutral sentences and 12 of the ambiguous aggressive sentences were taken from Coppello & Tata (1990). The additional 12 ambiguous sentences had been selected from a pool for plausibility then rated and agreed upon by six independent judges (Bond et al., unpublished data).

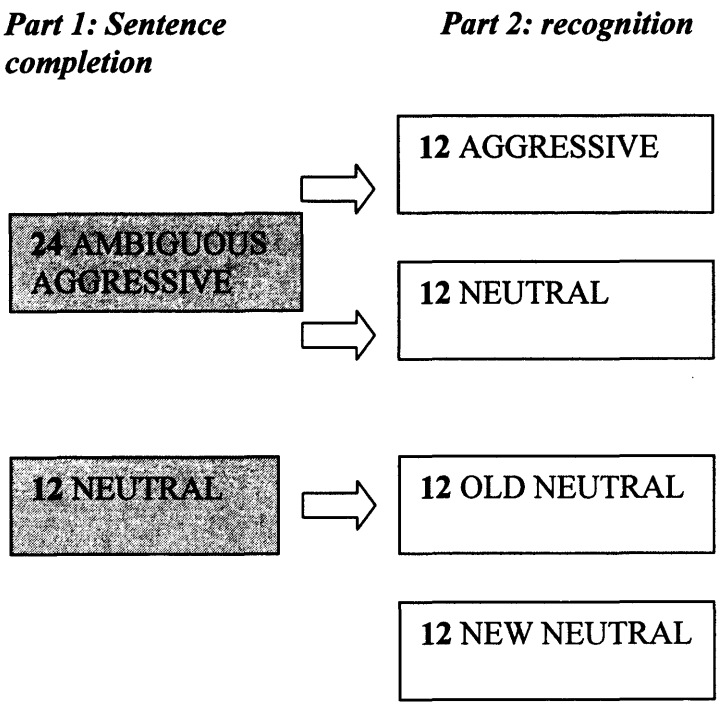
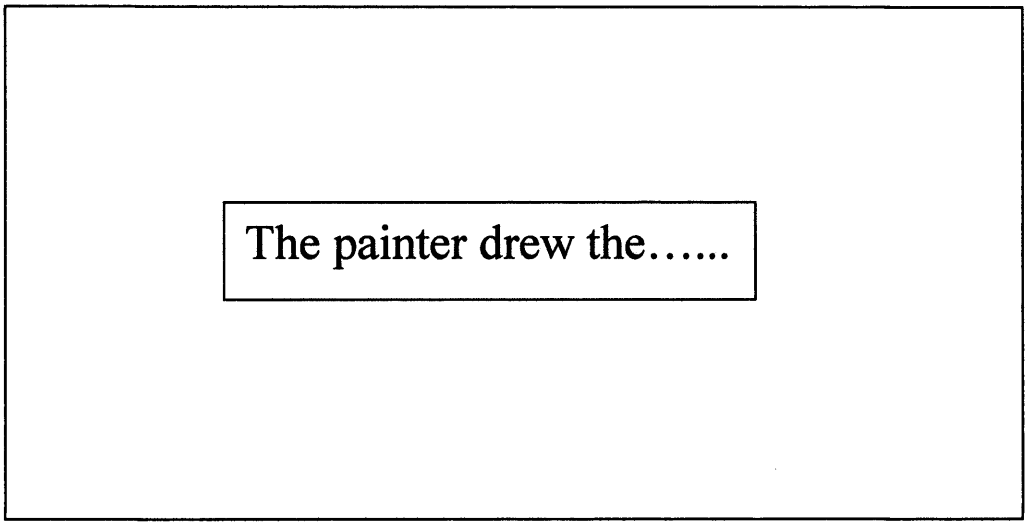


Figure 5.1: Schematic of sentences used in the sentence completion and recognition parts of the interpretative bias task

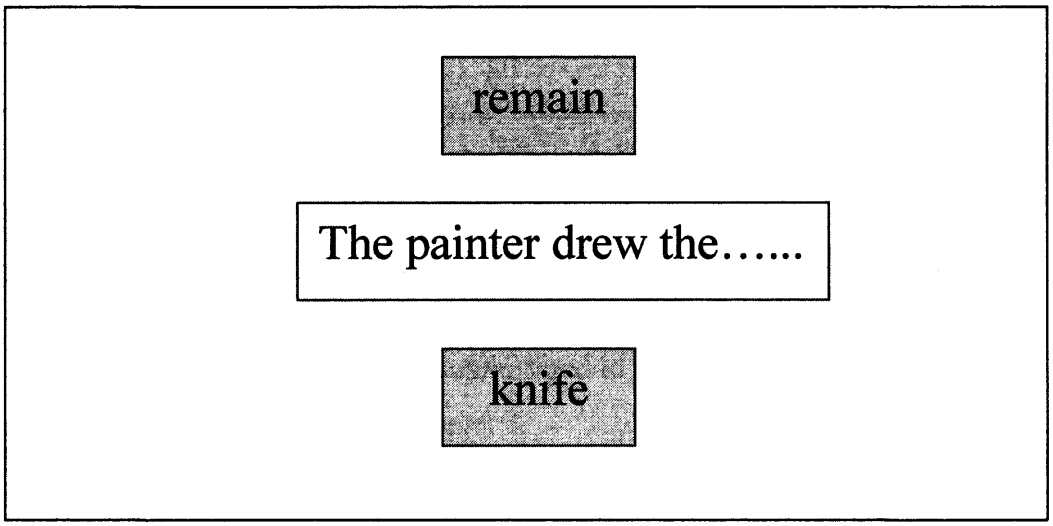
Part 1: Sentence completion (Figure 5.2a & b)

In the first part of the task the participants read the following instructions on the screen of a laptop computer: "A sentence will appear on the screen for a few seconds. The last word will be missing and instead you will see a dotted line _ _ _ _ _ _ _ _ . Following this, two words will appear: one on the upper part of the screen and one on the lower part of the screen. If you think the word on the upper part of the screen completes the sentence then press the top button. If you think that the word on the lower part of the screen completes the sentence, press the lower

button". The participants were then presented with 24 ambiguous and 36 neutral sentences in a pseudo-random order. The sentences were presented with the last word missing for 4s, followed by the presentation of two words, only one of which could meaningfully complete the sentence. Reaction time was recorded, and the next sentence appeared after the participant had responded. On completion of this part of the task, the participants were required to read allowed the numbers 100-0 which were displayed on the screen.



(a)



(b)

Figure 5.2: Schematic of Part 1 (sentence completion) of the interpretative bias task

Part 2: Recognition (Figure 5.3)

In the second part of the task, the following instructions appeared on the screen: "You will now see another series of sentences, one at a time. Some of these sentences will be **similar in meaning** to those shown previously. For each sentence Press 1 for NO, DEFINITELY NOT. You are **certain you did not see** a sentence with similar meaning before. Press 2 for NO, PROBABLY NOT. You think you **probably did not see** a sentence with similar meaning before. Press 3 for YES, PROBABLY DID. You think you **probably did see** a sentence with similar meaning before. Press 4 for YES, DEFINITELY DID. You are **certain you did see** a sentence with similar meaning before". The participants then responded to one practice sentence and were given the option to see the instructions again before carrying on with the task. The ratings were displayed at the top of the screen throughout the task. Both the ratings and reaction times to each sentence were recorded. Forty-eight sentences were presented at the rate of one every 10s.

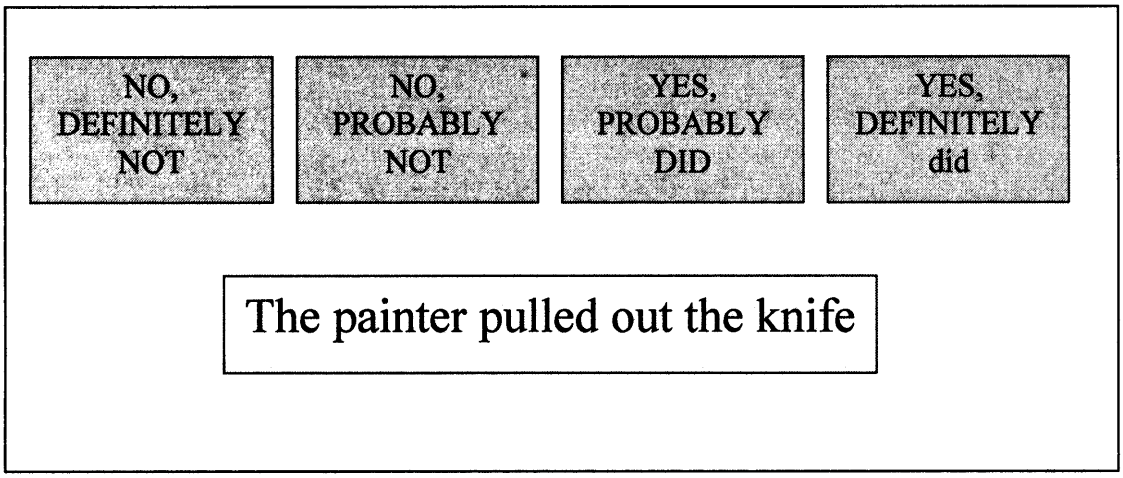


Figure 5.3: Schematic of part 2 (sentence recognition) of the interpretative bias task

The interpretative bias task was administered to participants at the end of the battery of cognitive tests described in chapter 3.

5.3 Statistical analysis

Statistical analysis was performed with SPSS version 11. Repeated measures ANOVA with group as a between subjects factor and sentence type (aggressive

versus neutral) as a within-subjects factor were used to analyse the interpretative bias task. One-way ANOVAs were used to compare levels of drug and alcohol use, as well as self-rated depression, anxiety, impulsivity and aggression. Where data violated the assumptions of normality, Kruskal-Wallis tests were used. Post hoc comparisons were performed with Sheffé tests, or in the case of variables compared using Kruskal-Wallis tests, individual Mann-Whitney U comparisons were carried out (α level Bonferroni corrected for multiple comparisons). Chi-squared tests were used to compare level of education and employment status, as well as the number of people reporting having ever tried and those currently regularly using recreational drugs. Pearson's correlations were used to explore the relationship between the interpretative bias task, drug use and mood. Due to the number of correlations performed an alpha level of 0.01 was adopted to minimise the probability of type I errors.

5.4 Results

5.4.1 Demographics

Of the 117 males aged 25-50 tested, 105 were included in the final analysis as the following were excluded: 5 ex-users (2 reported using ecstasy 6 months prior to testing, 2 urine screens positive for cocaine, 1 hair sample positive for MDMA), 1 current user (urine screen positive for cocaine), 1 poly-drug controls (urine screen positive for benzodiazepines) and 1 control (hair sample positive for MDMA). In addition, the data from the interpretative bias task was lost for 2 ex-users and 2 controls due to computer failure. Thus, the final data set comprised of 26 ex-ecstasy users, 25 current ecstasy users, 29 poly-drug controls and 25 drug-naïve controls.

There were no significant differences between the groups in age, pre-morbid IQ (Spot The Word), self-rated aggression (AQ), depression (BDI) or anxiety (STAI) (Table 5.1). A significant group difference was observed on self-rated impulsivity (BS total score) [$F(3,104)=2.79$, $p=0.045$). Post hoc tests revealed that the current users rated themselves as more impulsive than controls ($p=0.045$). Three ex-users, 2 current users, 5 poly drug controls and 1 control had received treatment for

depression or anxiety in the past. All groups had attained a similar level of education and employment status (Table 5.2).

5.4.2 Drug and alcohol use

No differences were observed between the groups in terms of the time since alcohol was last used, years of regular use and lifetime occasions of use (Table 5.3). However, a significant group difference was found on age of first use [$F(3,103)=5.80$, $p=0.016$]. Control participants started drinking at an older age than current users ($p=0.03$). There was also a group difference in units of alcohol consumed in a typical session [$F(3,103)=9.19$, $p=0.001$]. Both current users ($p=0.016$) and poly-drug controls ($p=0.001$) drank more units of alcohol per session than control participants[3].

One ex-user and 1 poly-drug control reported never having used cannabis. There were no group differences in time since last use, age of first use, years of regular use, days used per month, amount smoked per month or lifetime occasions of cannabis use. Table 5.4 shows percentages of each group reporting current regular use of cannabis and cocaine. Nine control participants had tried cannabis 1-3 times in their lifetime, between 1 and 10 years previously. Table 5.5 shows the group means (SD) for the use of cannabis, cocaine, amphetamines and LSD.

Significant group differences were observed in the time since last use of cocaine ($\chi2=15.75$, $df=2$, $p=0.001$) and LSD ($\chi2=21.31$, $df=2$, $p=0.001$). Current users had used cocaine more recently than both ex-users ($U=115.50$, $p<0.001$) and poly-drug controls ($U=146.00$, $p=0.003$), and LSD more recently than both ex-users ($U=76.00$, $p=0.001$) and poly-drug controls ($U=38.00$, $p=0.001$). One poly drug control and 1 control reported current regular use of amphetamines (≥1 day per month), 5 current users report current regular use of ketamine and 1 current user reported current regular use of LSD.

[3] Due to the significant group differences in units consumed in a typical session this variable was used as a covariate. This did not significantly affect on the results of the interpretative bias task and no significant interactions emerged with alcohol. Thus, these results are not reported.

	Ex-users	Current users	Poly-drug	Controls
Age (years)	29.46 (4.88)	28.64 (4.59)	31.93 (8.41)	32.28 (7.80)
Spot the Word	51.35 (3.85)	49.40 (4.26)	50.14 (4.36)	51.40 (3.44)
BDI	7.50 (5.69)	5.25 (3.44)	6.03 (4.17)	4.96 (5.50)
STAI	37.12 (9.15)	35.58 (7.71)	35.76 (6.93)	34.70 (8.22)
AQ	69.08 (16.70)	64.60 (15.48)	69.79 (15.20)	64.72 (17.44)
BS	54.35 (16.16)	60.80 (13.58)*	54.34 (14.75)	48.80 (14.58)

*significantly higher than controls, $p<0.05$

Table 5.1: Group means (SD) for age, pre-morbid IQ (Spot the Word), depression (BDI), anxiety (STAI), aggression (AQ) and impulsivity (BS)

Employment	Ex-users	Current users	Poly-drug	Controls
Unemployed	19%	16%	10%	16%
Part time	4%	8%	4%	8%
Full time	35%	56%	62%	56%
Student	23%	4%	10%	12%
Freelance	19%	16%	14%	8%
Education				
Up to16	4%	0%	7%	4%
GCSE	4%	8%	17%	8%
A Levels	11%	24%	24%	16%
Degree level	81%	68%	52%	72%

Table 5.2: Percentages of participants in each group in different types of employment and percentages reaching each level of education

Alcohol	Ex-ecstasy users (EE)	Current ecstasy users (CE)	Poly-drug controls (PC)	Drug-naïve controls (C)	Significant comparisons
Time since last use (days)	10.50 (33.55)	2.12 (1.56)	3.59 (2.91)	6.59 (15.32)	
Age of first use	14.67 (2.59)	13.76 (2.83)	14.47 (1.94)	16.33 (1.86)	
Years of regular use	10.91 (4.94)	9.34 (4.81)	14.43 (9.09)	12.38 (8.48)	
No. of days used in a typical month	10.43 (7.53)	13.28 (7.82)	10.87 (6.17)	7.90 (5.91)	
Amount in a typical session (units)	6.98 (3.26)	8.84 (4.74)	9.29 (3.56)	4.44 (3.60)	CE > C PC > C
Lifetime occasions	1312. (1160)	1385 (901)	1944 (1751)	1086 (1310)	

Table 5.3: Means (SD) of alcohol use variables in ex-ecstasy users, current ecstasy users, poly-drug controls and drug-naïve controls

	Ex-users	Current users	Poly-drug
Cannabis	28%	56%	43%
Cocaine	8%	64%	32%

Table 5.4: Percentage of participants in the drug using groups reporting current regular use of cannabis and cocaine.

There were several significant differences between ex-users and current users in terms of amount of ecstasy used (Table 5.6). As would be expected time since last use was significantly greater in ex-users ($U=0.00$, $p<0.001$). In addition, current users had used ecstasy regularly for more years ($U=171.50$, $p=0.04$) and had taken more on the occasion they had taken the most tablets in one session ($U=152.50$, $p=0.001$) than ex-users. On the other hand, ex-users took ecstasy more frequently when they had used it regularly than current users ($U=159.50$, $p=0.002$).

Cannabis	**Ex-ecstasy users (EE)**	**Current ecstasy users (CE)**	**Poly-drug controls (PC)**	**Significant comparisons**
Time since last use (days)	433.56 (719.57)	49.28 (147.08)	298.94 (531.38)	
Age of first use	16.65 (1.92)	16.12 (2.86)	15.96 (2.71)	
Years of regular use	8.34 (4.72)	9.93 (6.35)	10.62 (9.23)	
No. of days used in a typical month	16.70 (11.72)	16.35 (11.37)	17.24 (11.42)	
Amount used per month (oz.)	1.45 (1.72)	1.06 (1.16)	1.61 (1.88)	
Cocaine				
Time since last use (days)	807.81 (864.39)	27.52 (47.71)	594.27 (951.00)	CE > EE CE > PC
Age of first use	21.73 (2.44)	20.84 (3.35)	22.67 (5.89)	
Years of regular use	3.58 (1.80)	4.01 (3.28)	4.64 (3.48)	
No. of days used in a typical month	7.42 (9.06)	3.48 (3.31)	5.03 (7.12)	
Amount in a typical session (grams)	1.79 (1.92)	0.58 (0.38)	0.91 (0.70)	
Amphetamine				
Time since last use (days)	2410.65 (1902.59)	842.08 (1241.20)	2142.20 (2605.81)	
Age of first use	19.02 (2.17)	18.33 (3.82)	18.54 (3.61)	
Years of regular use	2.85 (2.38)	4.33 (5.90)	4.18 (5.63)	
No. of days used in a typical month	4.05 (5.65)	3.50 (2.37)	6.85 (7.18)	
Amount in a typical session (grams)	1.27 (1.03)	0.72 (0.43)	0.84 (0.49)	
LSD				
Time since last use (days)	1826.95 (1354.37)	522.09 (778.04)	2664.50 (2290.45)	CE > EE CE > PC
Age of first use	18.60 (3.15)	18.13 (3.72)	19.42 (4.24)	
Years of regular use	2.85 (1.65)	5.25 (4.17)	2.94 (1.67)	
No. of days used in a typical month	4.25 (3.58)	1.50 (0.58)	3.93 (4.31)	
Amount in a typical session (trips)	1.70 (0.89)	1.60 (0.65)	1.00 (0.46)	

Table 5.5: group means (SD) of cannabis, cocaine, amphetamines and LSD use

	Ex-users	**Current users**
Time since last use	987.30 (787.95)	14.20 (9.50)
Age of first use	19.48 (2.98)	18.20 (3.23)
Years of regular use	3.88 (2.30)	7.28 (4.70)**
Number of days used in a typical month	5.35 (3.22)	2.92 (2.16)
Amount used in a typical session (tablets)	2.52 (1.46)	3.86 (2.39)
Lifetime occasions	253.33 (230.20)	288.00 (420.88)
Highest number of tablets one session	5.35 (3.90)	10.54 (8.39)**

**p<0.01

Table 5.6: Mean (SD) of ecstasy use variables reported by ex and current ecstasy users

Urine samples were tested for cannabis, MDMA, amphetamine, cocaine, opiates, benzodiazepines and LSD. The samples for 2 ex-users, 3 poly-drug controls and 8 controls were not available due to sample contamination or laboratory error. Participants were excluded if they tested positive for any drug other than cannabis. The following percentage of each group tested positive for cannabis: ex-users – 17%, current users – 72%, poly drug controls – 20%, controls – 0%.

5.4.3 Interpretative bias task (Table 5.7)

Part1: sentence processing

A significant main effect of sentence type was found [$F(1,101)=109.35$, $p<0.001$] indicating that all groups processed neutral sentences faster than aggressive sentences. There was no main effect of group or group x sentence type interaction.

Part 2: recognition

A significant main effect of sentence type was found in the reaction time to correctly recognised sentences [$F(1,101)=10.32$, $p=0.002$). Neutral sentences were recognised faster than aggressive sentences. There was no main effect of group or group x sentence type interaction. The same pattern was found for the total number of sentences correctly recognised [$F(1,101)=43.98$, $p<0.001$] and how confident

participants were in their choices [$F(1,101)=18.09$, $p<0.001$]: more neutral sentences were recognised than aggressive, and participants were more confident in their recognition of neutral sentences then aggressive ones. Once again no main effects of group or group x sentence type interactions were observed. No significant differences were found for sentences participants incorrectly endorsed as unseen, and no significant differences were found in the recognition of previously seen, unambiguously neutral sentences.

As Bond et al's (2004) findings suggested that all drug users have increased bias toward aggressive material the drug using groups were combined and compared to the control group. Again, no significant interactions or main effects of group were observed.

5.4.4 Correlations

All groups combined: Years of regular alcohol use correlated with the differences between reaction times to aggressive and neutral sentences in the interpretative bias task (rho=0.26, p=0.008), while verbal aggression tended to correlate negatively with age of first use of alcohol (r=-0.23, p=0.03). Reaction time to complete aggressive sentences tended to correlate negatively with motor impulsivity (r=-0.22, p=0.022) while total number of neutral sentences recognised in the second part of the task tended to correlate negatively with cognitive impulsivity (r=-0.20, p=0.04)

Drug using groups combined: Number of days per month amphetamines were used correlated with reaction time to neutral sentences in both the first (r=0.42, p=0.006) and the second (r=0.38, p=0.01) part of the interpretative bias task. In addition, the age of first use of cocaine tended to correlate with verbal aggression (r=-0.24, p=0.045).

Ecstasy using groups combined: Time since ecstasy was last used correlated with number of neutral sentences recognised in the second part of the task (rho=0.36, p=0.009). No other measure of ecstasy use correlated with the interpretative bias task or any sub-scale of the AQ.

	Ex-users	*Current users*	*Poly-drug*	*Controls*
	Part 1: reaction time to completion of sentences			
Aggressive	1233.00 (307.45)	1264.16 (457.01)	1477.62 (517.16)	1389.32 (391.50)
Neutral	1050.73 (251.41)	1046.16 (285.07)	1220.17 (413.52)	1122.28 (307.51)
	Part 2: response time to sentences endorsed as seen			
Aggressive	3851.42 (1037.49)	3751.64 (650.54)	3737.24 (1003.33)	3983.28 (1101.99)
Neutral	3406.31 (690.75)	3518.88 (728.12)	3704.14 (910.06)	3438.16 (604.70)
	Part 2: confidence ratings of sentences endorsed as seen			
Aggressive	3.42 (0.48)	3.36 (0.40)	3.50 (0.82)	3.58 (0.47)
Neutral	3.79 (0.40)	3.56 (0.44)	3.78 (0.39)	3.78 (0.36)
	Part 2: number of sentences correctly recognised			
Aggressive	5.65 (2.37)	5.92 (2.64)	6.00 (2.71)	5.84 (2.94)
Neutral	8.19 (2.08)	7.28 (1.65)	7.83 (1.81)	7.84 (1.95)
	Part 2: reaction time to sentences endorsed as *not* seen			
Aggressive	3958.23 (762.31)	3969.32 (839.43)	4080.21 (1073.32)	3863.52 (1284.80)
Neutral	3843.12 (833.70)	3770.48 (859.90)	3661.07 (1270.29)	3929.88 (947.50)
	Part 2: confidence ratings of sentences endorsed as *not* seen			
Aggressive	1.37 (0.46)	1.32 (0.45)	1.52 (0.49)	1.26 (0.50)
Neutral	1.48 (0.50)	1.50 (0.46)	1.57 (0.51)	1.46 (0.45)
	Part 2: number of sentences incorrectly rejected			
Aggressive	6.19 (2.32)	6.08 (2.64)	5.83 (2.76)	6.00 (2.94)
Neutral	3.77 (2.01)	4.64 (1.66)	4.03 (1.88)	4.08 (2.04)
	Part 2: previously seen neutral sentences			
RT	3144.19 (554.98)	3269.12 (798.90)	3299.79 (777.33)	3204.28 (660.65)
Rating	3.92 (0.27)	3.88 (0.33)	3.78 (0.39)	3.92 (0.24)
No. correct	9.88 (1.51)	9.20 (1.44)	10.14 (1.51)	9.32 (2.25)

Table 5.7: Means (SD) for performance on the cognitive bias task in ex-ecstasy users, current ecstasy users, poly-drug controls and drug-naïve controls

5.4.5 Further investigation of ex and current ecstasy users

No significant group differences on the interpretative bias task or AQ scores were observed when comparing ecstasy users who reported increased negative effects of ecstasy use to those who reported decreased or constant negative effects.

5.5 Discussion

The main result from the present study is than no evidence was found for increased cognitive bias towards aggressive material in either current or ex-ecstasy users. All groups processed and recognised neutral sentences faster and more accurately than aggressive ones. In addition, there were no group differences in self-rated aggression.

Although Gerra et al. (2001) found evidence of increased aggression in ecstasy users abstinent for 3 weeks, it is likely that this result was related to the sample of ecstasy users tested and the inappropriate control group used. All groups in the present study were well matched in terms of depression, anxiety, pre-morbid IQ and education. Bond et al. (2004) also used an information processing approach, and found evidence of increased bias toward angry material in 3 groups of drug users regardless of whether they used ecstasy or not. Although there was no drug-naïve control group, the authors point out that overall, participants were faster to respond to material with an angry component than neutral material, the opposite pattern to that which has been observed in non-drug users. The present study however, found that all drug using groups responded in the same way as controls: they were faster and more accurate when responding to neutral material. Once again, these apparently opposing results could be explained by the sample of drug users tested.

The ecstasy using groups in Bond et al. (2004) rated themselves as more aggressive than the groups in the present study (ex users: 79.67 ±17.12 *vs.* 69.08 ±16.70, current users: 72.63 ±15.25 *vs.* 64.60 ±15.48). In addition, the cut off score for the BDI for exclusion from the study was higher than that of the present study, and no information was provided about *past* depression or anxiety, all factors which may affect processing of angry information.

The lack of group differences could be due to task used not being sensitive enough to identify differences in aggressive cognitive bias. However, this seems unlikely as group differences in mid-week aggression have been found between ecstasy users and controls with same task in 2 different samples (Curran et al., 2004; Chapter 6 – Hoshi et al., 2006). One of the most interesting aspects of these findings is that they support the idea that the increased aggression found in ecstasy users 3 or 4 days following use of the drug is a *transient* phenomenon as the current users in the present study, who have not taken the ecstasy for an average of approximately 2 weeks, do not show increased aggression. In addition, Curran et al. (2004) found no differences in self-rated aggression 7 days after ecstasy use.

Interestingly, there was a tendency for task performance to correlate with both impulsivity scores and alcohol use across the groups. Impulsivity and aggression often occur concurrently (see section 1.5.3), and a link between alcohol and aggression has previously been demonstrated, both acutely in men (e.g. Gussler-Burkhardt & Giancola, 2005) and in alcohol abusers (e.g. Dom et al., 2006). This suggests that alcohol use and levels of impulsivity may be better predictors of aggression than ecstasy use. While there was one correlation between ecstasy use and the interpretative bias task in the 2 ecstasy using groups, correlations between aggression and both cocaine and amphetamine use were apparent across *all* the drug using groups. These correlations emphasise the importance of matching for the use of other recreational drugs, especially other stimulants, when investigating the long-term effects of ecstasy use. Of course, caution must be exercised when interpreting purely correlational evidence, especially as many of these correlations failed to reach the chosen, stricter significance level of 0.01.

The possibility of increased aggression in ecstasy users has been investigated based on the suspected changes in serotonergic function following the consumption of MDMA in ecstasy tablets, and the link between 5-HT and aggression (see section 1.5.2). However, very few studies employ a measure of 5-HT function. Curran & Verheyden (2003) administered a tryptophan challenge to participants and found that ex-users had significantly higher plasma tryptophan following tryptophan augmentation than both current users and poly-drug controls. The ex-users also had

deficits in cognitive function and scored higher on the AQ. It is possible that a certain sub-group of ecstasy users are more susceptible to MDMA-induced alterations of the serotonergic system, and are therefore more susceptible to psychological problems such as increased aggression. These differences in susceptibility could explain the conflicting nature of the findings in the ecstasy literature. The nature of this distinction is, however, far from clear. Thomasius et al. (2003) found no difference in serotonin transporter density in ex-ecstasy users compared to controls and yet results showed that the ex-users had both higher levels of psychopathology, including aggression, and impaired cognitive function when compared to controls. An intriguing piece of new research suggests that there may be a genetic component. Roiser et al. (2005a) assessed emotional processing and depression in 66 ecstasy users, 30 cannabis users and 28 control participants using an affective go/no go task and the BDI. They also assessed each participants 5-HT transporter gene-linked polymorphism, which produces 2 alleles: '*l*' (long) and '*s*' (short). As no significant differences in performance on the task or in BDI scores were found between in the cannabis users and the controls, or when genetic sub-groups were compared within the groups, these 2 groups were pooled and compared to the ecstasy users. There were a similar number of each genetic subgroup (*ll*, *ls*, *ss*) in each group which the authors interpreted as indicating that this genetic variation was not a predictor of ecstasy use. Although there were no group differences in responses to happy and sad words, the results showed that the *ll* subgroup of the ecstasy users made fewer commission errors in blocks where the target was not changed. This pattern has been previously found in healthy controls, and all genetic subgroups of the control group also showed this pattern. However, the *ls* and *ss* subgroups of the ecstasy users did not make this expected reduction. Previous research suggests that having the s allele is associated with increased susceptibility to affective disorders such as bipolar and unipolar depression (Furlong et al., 1998), and that it has been shown to predict poor response to antidepressants such as fluvoxamine (Smeraldi et al., 1998). Given these findings, it is possible that individuals with the *s* allele are more susceptible to mood disorders such as depression and aggression following ecstasy use. This reasoning could also be applied to cognitive deficits following ecstasy use (see Section 4.5).

In summary, this study found no evidence of differences in self-rated aggression or cognitive bias towards aggressive material between current ecstasy users, ex-ecstasy users, poly-drug controls and drug-naïve controls. These findings provide support for previous research suggesting that increased aggressive bias observed in ecstasy users several days after taking the drug is a transient phenomenon.

Chapter 6: Ecstasy, gender and mid-week aggression

An investigation into aggressive interpretative bias 4 days after ecstasy use in both male and female ecstasy users

6.1 Introduction

"But, the real come down is on the Monday and the Tuesday when you're back to reality....sometimes I can be really snappy with my husband.....but then, like, by Wednesday I'm fine again. Tuesdays! Tuesday's the worst day"

Fiona, 27 year old, uses ecstasy on Friday nights. Quoted in Hammersley et al. (2002)

Low 5-HT is known to be associated with depression and aggression (see sections 1.5.1 & 1.5.2). Increasingly, research evidence supports the existence of the 'mid-week blues', a lowering of mood several days after ecstasy use (see section 1.8.1) which may reflect MDMA induced depletion of 5-HT and inhibition of TPH. In addition, 2 recent club-based studies have demonstrated that self-rated aggression follows the same pattern as had been demonstrated with depression scores: ecstasy users rated themselves as being less aggressive shortly after taking the drug but more aggressive a few days later compared to non-using controls (Hoshi et al., 2004; Verheyden et al., 2002). However, as discussed in the previous chapter, demand characteristics associated with using self-rating scales may influence the pattern of results. Ecstasy users' preconceptions about the 'mid-week blues', or 'moody Tuesday' phenomena (that are well known among ecstasy users) may affect their responses when presented with scales that make no attempt to disguise what they are tapping. It is also possible that, rather than arising from some neurochemical change, the ecstasy users simply have a better time at the weekend and thus find the routine of the week depressing:

> *"By dancing all night on E, a feeling of total bliss and utter fulfilment is achieved, and of course the downside to this is that nothing else beats that feeling, thus reality can seem boring" (quoted in Saunders, 1995)*

Previously we aimed to overcome these problems by using an objective information processing approach to assessing aggressive bias (Curran et al., 2004). Participants were presented with the same interpretative bias task described in Chapter 5. Ecstasy users and controls carried out the task 4 days after an initial test session in which the ecstasy users had taken the drug in clubs or parties. The pattern of results on this task showed that a few days after ecstasy use, ecstasy users were cognitively biased towards interpreting ambiguous information in an aggressive way. They processed possibly aggressive sentences quicker than neutral ones and were more confident in recognising aggressive interpretations. In contrast, the controls were cognitively biased towards neutral interpretations in both their response times and recognition confidence ratings. Given that controls were also recreational drug users, the increased aggressive bias of ecstasy users appeared to relate to their ecstasy use specifically rather than general club drug use. Indeed, frequency of ecstasy use was positively correlated with degree of aggressive cognitive bias.

The main aim of the present study was to determine the robustness of these intriguing findings by attempting to replicate Curran et al.'s (2004) study. A new sample of ecstasy users and controls were therefore recruited and assessed following procedures identical to Curran et al. (2004). A subsidiary aim was to explore the possibility of gender differences in the relationship between aggressive interpretative bias and ecstasy use, as the predominance of males in our previous study did not allow for gender comparisons. There are gender differences in the expression of aggression (Newman et al., 1998; Nunn & Thomas, 1999). Further, there is some preliminary evidence that women may be more sensitive to acute MDMA effects (Liechti et al., 2001a) and to the neurobiological effects of MDMA as measured by serotonin transporter densities (Buchert et al., 2004; Reneman et al., 2001a). I took advantage of the opportunity to combine our new data set with that

of Curran et al. (2004), which could allow sufficient participant numbers to explore gender differences.

6.2 Materials and Methods

6.2.1 Design and Participants

Ecstasy users were compared to controls on the night of drug use (day 0) and 4 days later using an independent groups, repeated measures design. Participants were recruited using the 'snowball technique' (Solowij et al., 1992). To ensure that the participants' judgement was not impaired following drug use with regards to consenting to take part in the study, written, informed consent was obtained on both day 0 and day 4. Participants were tested following an identical procedure to that described in Curran et al. (2004). The study was approved by the institutional ethics committee (see Appendix 6 for ethics approval and information sheet).

6.2.2 Procedure

On the first night of the study (day 0) participants were tested in clubs or parties. After agreeing to take part they were taken individually to a quiet area where they read the volunteer information sheet and gave written consent. After completing the self-rating assessments of mood states outlined below, a time was arranged to follow up the participant on day 4. This usually took place at the participants' homes, where once again written informed consent was obtained. The same set of self-rated mood assessments was completed as on day 0, as well as assessments of trait mood and an interpretative bias computer task, all described below. The participants' pulse was taken on both days 0 and 4.

6.2.2(i) State mood and subjective effects assessments – days 0 & 4

Visual analogue scales were used to assess current (or state) mood on both days of the study: the Aggression Rating Scale (ARS; Bond & Lader, 1986), the Mood Rating Scale (MRS; Bond & Lader, 1974) and a subjective effects scale (SES) tailored to include typical subjective effects experienced after ecstasy use. This scale included additional items added following Curran et al. (2004) designed to tap more of the known empathic effects of MDMA. A modified Beck Depression Inventory (BDI; Beck, 1978) designed to tap how the participants had been feeling

over the last three days (Curran & Travill, 1997) was also administered at both test sessions.

6.3.3(ii) Interpretative bias task – day 4

The task, procedure and instructions followed exactly those used by Curran et al., (2004) and is described in detail in section 5.2.2(i). The stimuli for the first part of the task consisted of 36 unambiguous neutral sentences interspersed with 24 ambiguous sentences, which could be interpreted as either aggressive or neutral (e.g. "The painter drew the knife"). For the recognition task, 72 sentences were prepared, 48 of which were presented to any given subject. For the ambiguous sentences, 24 disambiguated versions were presented: 12 consistent with an aggressive interpretation (e.g. "The painter pulled out the knife") and 12 consistent with a neutral interpretation (e.g. "The painter sketched the knife"). The remaining 24 sentences consisted of 12 neutral sentences with the same meanings (but slightly different wording) to those presented previously and 12 new unambiguous neutral sentences. Half of the participants in each group were presented with one set of disambiguated sentences and the other half the opposite set.

Part 1: Sentence processing

In the first part of the task the participants were presented with the 24 ambiguous and 36 neutral sentences on a laptop computer, one at a time for 4 seconds. The last word of the sentence was missing. After each incomplete sentence two words appeared simultaneously on the screen and participants were required to choose the word that meaningfully completed the sentence (only one of the words could do this). Reaction time was recorded. Immediately after completing this part of the task, a filler task was given whereby the participants were required to read aloud the numbers 100-0 which were displayed on the screen.

Part 2: Recognition memory

In the second part of the task 48 sentences were presented at the rate of one every 10s. Participants were asked to rate how confident they were about whether they had seen a sentence with a similar meaning in the first part of the task or not. They responded on a four-point scale: 1 = definitely not, 2 = probably not, 3 = probably

yes and 4 = definitely yes. Both the ratings and reaction times to each sentence were recorded automatically.

6.2.2(iii) Other assessments on day 4

The Hospital Anxiety and Depression scale (HADS; (Zigmond & Snaith, 1983) was used to index trait anxiety and depression, and trait aggression was indexed using the Aggression Questionnaire (AQ; Buss & Perry, 1992). A drug use history interview was carried out to assess amount, frequency and duration of use of other psychotropic drugs, and details of drugs used on day 0 and on days 1-3 (if any) were also recorded. Demographic information (age, educational background and employment) was also collected on day 4.

6.3 Statistical analysis

Repeated measures analysis of variance (ANOVA) with group (ecstasy versus controls) as a between subjects factor and sentence type (aggressive versus neutral) as a within-subjects factor were used to analyse the interpretative bias task. Repeated measures ANOVA was also used on self-rating scores obtained on both days (BDI, ARS, MRS and SES), with group as a between subjects variable and day (day 0 versus day 4) as a within-subjects variable. The ARS is comprised of 13 variables that showed high internal consistency both on day 0 (Cronbach's $\propto$ = 0.92) and day 4 ($\propto$ = 0.95). Thus, a mean aggression score was calculated and used in subsequent analyses. Univariate ANOVAs were used to compare groups and genders on aggression (AQ), depression (Had-D), anxiety (Had-A), age and drug use apart from some measures of drug use where Mann-Whitney U-tests (two-tailed) were used due to non-parametric data. Chi-square was used to assess if there was a gender imbalance between the groups. Pearson product-moment correlations were used to examine the relationship between aggression (both self-rated and measures from the computer task) and drug use. For the analysis of the combined data set, gender was included as an additional between subjects factor in order to investigate the possibility of gender differences. Further correlations between ecstasy use and aggression measures were carried out separately for males and females on the basis in that a previous study (Verheyden et al, 2002) the

correlations varied by gender. All data were analysed using SPSS for Windows version 11.0.

6.4 Results

Results are reported in 2 parts: firstly, the results from the new data set (1a), and secondly the results from the new data set combined with Curran et al (2004) (1b).

6.4.1 Part 1(a): Replication study

6.4.1(i) Demographics

In total 46 participants aged between 18-23 years completed the study on both test days: 19 ecstasy users (11 males and 8 females) and 27 controls (17 males and 10 females). The control group were mainly ecstasy-naïve, although 2 had previously tried the drug once. The majority of the participants were undergraduate students. There were no group differences in gender, age, trait aggression (AQ), depression (Had-D) or anxiety (Had-A) (Table 6.1).

Levels of use of ecstasy, alcohol and cannabis are given in Table 6.1. All participants drank alcohol regularly. Cannabis was used ≥1 day per month by 15/19 ecstasy users and 17/27 controls. There was a group difference in frequency of cannabis use (U=142.00, p=009, two-tailed) showing that ecstasy users smoked cannabis on more days per month than controls (9.73 ±8.01 vs. 3.67 ±4.49). Four ecstasy users and 1 control used cocaine, 5 ecstasy users and 4 controls used amphetamines and 2 ecstasy users used ketamine occasionally. A significant group difference in the amount of alcohol that was consumed on day 0 (U=160.50, p=0.031, two-tailed) indicated that the control group drank more units of alcohol on day 0 than ecstasy users (9.44 ±6.74 vs. 5.47 ±4.97). Other drug use on day 0 included 11 ecstasy users and 5 controls smoking cannabis and cocaine was used by 2 ecstasy users. There were no significant differences in amount of cannabis or alcohol consumed in the days between the test sessions (days 1-3). Despite having been asked to refrain from alcohol and drug use on day 4, 3 ecstasy users and 2 controls had drunk alcohol (2-4 units) and 6 ecstasy users and 1 control had smoked cannabis (sharing 1-3 joints) prior to testing (Table 6.1).

Aggression, anxiety, depression, age	**Ecstasy users**	**Controls**
AQ	73.84 (18.19)	70.30 (12.31)
HAD-A	7.84 (4.06)	7.37 (3.53)
HAD-D	3.42 (2.46)	3.33 (2.37)
Age	20.21 (1.55)	20.63 (0.79)
Drug use		
Ecstasy frequency (days per month)	2.53 (1.31)	-
Ecstasy typical dose (tablets)	3.05 (0.96)	-
Ecstasy length of use (years)	2.47 (1.67)	-
Ecstasy use day 0 (tablets)	2.45 (0.78)	
Alcohol frequency (days per month)	11.58 (3.86)	11.11 (4.34)
Alcohol typical dose (units)	7.79 (3.68)	9.48 (4.15)
Alcohol length of use (years)	5.16 (2.32)	5.52 (1.78)
Alcohol day 0 (units)	**5.47 (4.97)**	**9.44 (6.74)***
Alcohol days 1-3 (units)	3.37 (3.39)	3.44 (4.77)
Alcohol day 4 (units)	0.53 (1.31)	0.15 (0.53)
Cannabis frequency (days per month)	**9.74 (8.01)**	**3.67 (4.49)****
Cannabis monthly use (oz)	1.66 (1.23)	1.22 (1.01)
Cannabis length of use (years)	3.32 (2.69)	2.52 (2.17)
Cannabis day 0 (joints)	1.47 (1.58)	0.26 (0.59)
Cannabis days 1-3 (joints)	1.42 (1.61)	0.37 (0.79)
Cannabis day 4 (joints)	0.58 (0.96)	0.04 (0.19)

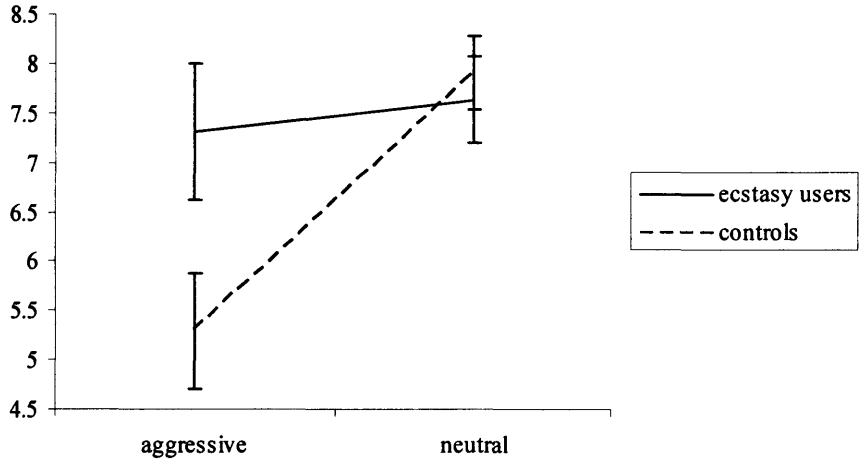
***p<0.05 **p<0.01**

Table 6.1: Group means (SD) of aggression (AQ), anxiety (Had-A), depression (Had-D) and age, and of frequency, dose and length of ecstasy, cannabis and alcohol use.

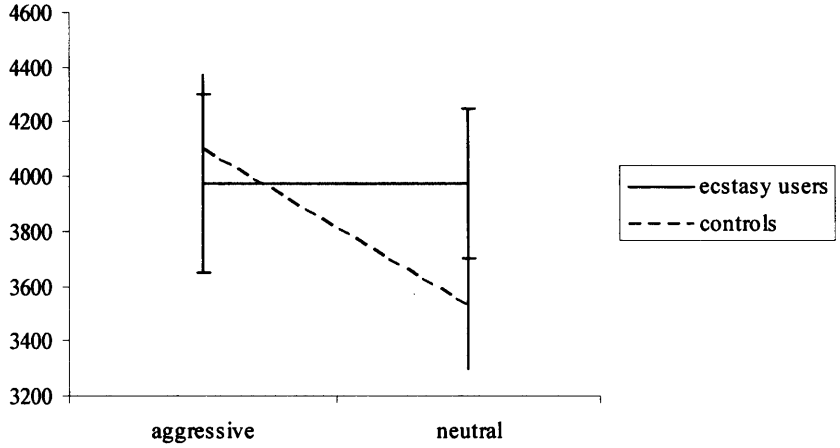
6.4.1(ii) Interpretative Bias Task

Part 1. Sentence processing: No group or sentence type differences emerged in the time to complete ambiguously aggressive and neutral sentences.

Part 2. Recognition memory: A significant group x sentence type interaction [F(1,44)=6.24, p=0.016] and a main effect of sentence type [F(1,44)=10.25, p=0.003] was found for the number of sentences correctly identified as being seen in the first part of the task (Fig. 1a). Ecstasy users recognised more disambiguated aggressive sentences than controls; both groups recognised similar amounts of neutral sentences. No significant group or sentence type differences were found in how confident the participants were in recognising previously seen sentences. In addition, the speed of judging whether sentences with a similar meaning had been seen in the first part of the task showed a trend towards a significant group x sentence type interaction [F(1,44)=2.27, p=0.078]. Ecstasy users tended to react slower to neutral sentences than controls, where as both groups showed similar reaction times to aggressive sentences (Fig. 1b). No significant differences were found in the recognition of previously seen, unambiguously neutral sentences.



(a)



(b)

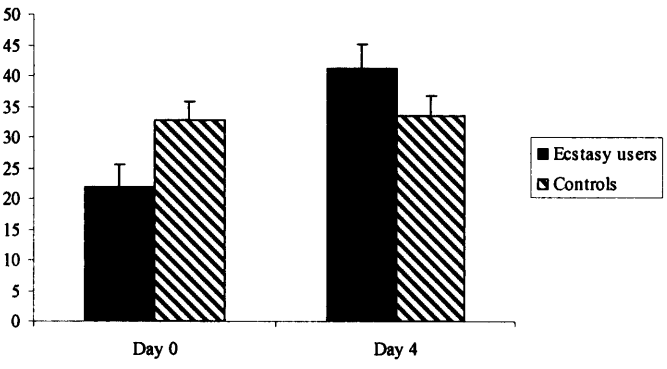
Figure 6.1: Mean (SE) (a) number of sentences correctly recognised by ecstasy users and controls (b) reaction times for recognition of aggressive and neutral sentences

6.4.1(iii) Aggression Rating Scale

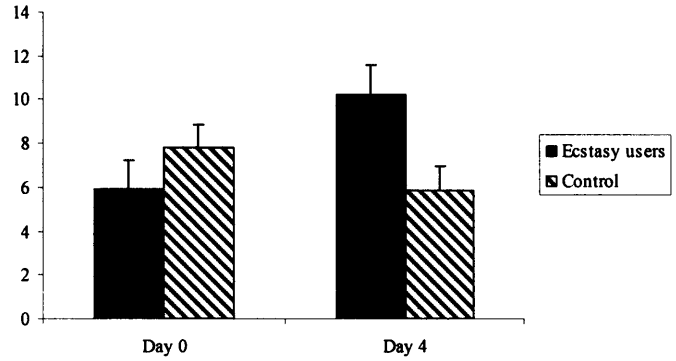
Self-rated aggression showed a significant group x day interaction [$F(1,44)=15.13$, $p<0.001$] and a main effect of day [$F(1,44)=17.34$, $p<0.001$]. Ecstasy users rated themselves as less aggressive than controls on day 0 and more aggressive than them on day 4 (Fig. 6.2a).

6.4.1(iv) Beck Depression Inventory:

Self-rated depression also showed a group x day interaction [$F(1,44)=31.36$, $p<0.001$] and a main effect of day [$F(1,44)=4.28$, $p=0.044$]. Ecstasy users rated themselves as less depressed than controls on day 0 and more depressed on day 4 (Fig. 6.2b).



(a)



(b)

Figure 6.2: Mean and SEM (a) aggression (ARS) scores and (b) depression (BDI) scores for ecstasy users and controls on day 0 and day 4

6.4.1(v) Mood rating scale (Table 6.2)

The MRS is condensed into 3 factors: sedation, discontentedness and anxiety.

Sedation: A main effect of day was found [$F(1,44)=10.28$, $p=0.003$] showing that both groups rated themselves as more sedated on day 4 than on day 0.

Discontentedness: There was a significant group x day interaction [$F(1,44)=4.65$, $p=0.036$] and a main effect of day was found [$F(1,44)=7.49$, $p=0.009$]. While both groups rated themselves as more discontented on day 4, the controls were less contented than the ecstasy users on day 0 and more contented than them on day 4.

Anxiety: A group x day interaction was found [$F(1,44)=11.25$, $p=0.002$] as well as a main effect of day [$F(1,44)=21.33$, $p<0.001$]. Ecstasy users rated themselves as more anxious than controls on day 0, while the 2 groups had similar levels on day 4.

	Ecstasy users		Controls	
	Day 0	***Day 4***	***Day 0***	***Day 4***
MRS 1 – sedation	48.87 (6.71)	52.72 (6.08)	47.49 (7.09)	51.30 (4.48)
MRS 2 – discontentedness	44.86 (7.61)	52.37 (7.10)	48.62 (6.56)	49.51 (5.14)
MRS 3 - anxiety	65.63 (20.01)	46.95 (12.46)	52.70 (14.04)	49.74 (8.12)

Table 6.2: Means (SD) for the 3 Mood Rating Scale factors (sedation, discontentedness and anxiety) for ecstasy users and controls on day 0 and day 4

6.4.1(vi) Pulse (Table 6.2)

A significant day x group interaction [$F(1,44)=26.51$, $p<0.001$] and a main effect of day [$F(1,44)=41.34$, $p<0.001$] were found reflecting much faster pulse rate in

ecstasy users than in controls on day 0 (95.5 ±13.7 vs. 75.0 ±10.3) and similar rates in both groups on day 4 (76.1 ±8.3 vs. 72.8 ±9.4).

6.4.1(vii) Subjective effects scales (SES)

As the SES comprises 26 sub-scales a more stringent alpha level of 0.01 was adopted to reduce the likelihood of type I errors. Fifteen items showed a significant day x group interaction, all reflecting ecstasy users rating themselves as higher than controls on day 0 but similar on day 4. These scales included affective items [euphoria ($p<0.001$); closeness to others ($p<0.001$); openness to others ($p=0.001$)], somatic items [teeth grinding ($p<0.001$); dry mouth ($p<0.001$); blurred vision ($p=0.001$); jaw clenching ($p<0.001$); thirsty ($p<0.001$); loss of appetite ($p=0.007$)] and cognitive items [lack of concentration ($p=0.004$); memory problems ($p=0.004$); sensitive to colour ($p<0.001$)] (see Appendix 7 for descriptive data).

6.4.1(viii) Correlations

In the ecstasy group a negative correlation was found between frequency of ecstasy use and total number of neutral sentences recognised in the second part of the interpretative bias task ($r=-0.47$, $p=0.043$). Again within the ecstasy group a correlation was found between the 'anger' sub-scale of the AQ and the total number of aggressive sentences recognised in the second part of the task ($r=0.512$, $p=0.025$). This scale of the AQ also correlated with response time to neutral sentences in the control group ($r=0.394$, $p=0.042$). In the control group years of alcohol use was correlated with response time to recognising aggressive sentences ($r=0.556$, $p=0.003$), frequency of alcohol use was correlated with total scores on the AQ ($r=0.397$, $p=0.04$).

6.4.2 Part 1(b): Combined data set exploring gender differences

6.4.2(i) Demographics

The combined data set produced a total of 107 participants aged between 19-24 years who completed the study on both test days: 48 ecstasy users (31 males and 17 females) and 59 controls (35 males and 24 females). The control group was made up mainly of those who were ecstasy-naïve, although 2 had previously tried the drug once. Four participants in the ecstasy group were starting university courses

the following term and 2 were in full time employment. All other participants were undergraduate or postgraduate students. There were no group differences in gender, age, trait aggression (AQ), depression (Had-D) or anxiety (Had-A) and no group x gender interactions, although there was a main effect of gender [$F(1,103)=6.24$, $p=0.014$] whereby females self-rated higher anxiety levels than males (7.63 ±3.69 vs. 5.88 ±3.60) (Table 6.2). There were no significant differences when comparing gender in each group (i.e. female ecstasy users vs. female controls and male ecstasy users vs. male controls).

Ecstasy use by males and females is given in Table 6.2(a). Males reported using significantly more tablets in a typical session than females ([$F(1,46)=5.04$, $p=0.03$]; there were no differences in frequency (days per month) or years of use. There were no group differences or group x gender interactions in the use of cannabis or alcohol (Table 6.2a&b). All participants drank alcohol regularly and 35/48 ecstasy users and 42/59 controls regularly smoked cannabis. There was a main effect of gender showing that males drank more units of alcohol per session (7.75 ±4.37 vs. 5.54 ±2.50) [$F(1,103)=8.56$, $p=0.004$], on more days per month (11.97 ±5.62 vs. 9.56 ±4.80) [$F(1,103)=5.46$, $p=0.021$] and had drunk for longer (5.85 ±1.74 vs. 4.55 ±1.63) [$F(1,103)=18.28$, $p<0.001$] than females. In addition, a significant main effect of gender was found for number of days per month cannabis was used: again, males used more frequently than females (8.97 ±9.22vs. 5.24 ±5.49) [$F(1,103)=5.69$, $p=0.019$]. Eight males and 4 females in the ecstasy group, and 2 males in the control group used cocaine occasionally. One male ecstasy user and 2 male controls used amphetamines and 3 male ecstasy users used ketamine (all <1 day per month). On day 0, 44 ecstasy users and 52 controls drank alcohol, 30 ecstasy users and 16 controls smoked cannabis, 4 ecstasy users and 1 control used cocaine, 2 ecstasy users and 1 control used ketamine. In addition, between the two test sessions 31/48 ecstasy users and 34/59 controls consumed alcohol, and cannabis was used by 19/48 ecstasy users and 16/59 controls. Because of gender differences, alcohol use was covaried in the analysis of all measures reported below. However, no effect of this covariance was found on any measure, and no significant interactions were found between alcohol use and group or gender.

	Ecstasy users		
Aggression, anxiety, depression, age	Male	Female	Total
AQ	70.90 (15.19)	68.12 (16.92)	69.92 (15.70)
Had-A	5.71 (3.50)	8.12 (3.1)	6.56 (3.78)
Had-D	2.81 (2.41)	2.94 (1.92)	2.85 (2.23)
Age	21.19 (1.70)	20.65 (1.11)	21.00 (1.53)
Drug use			
Ecstasy frequency (days per month)	2.48 (1.18)	2.29 (0.77)	2.42 (1.05)
Ecstasy typical dose (tablets)	3.15 (1.48)*	2.29 (0.66)	2.84 (1.31)
Ecstasy length of use (years)	2.92 (1.70)	2.09 (0.92)	2.63 (1.51)
Alcohol frequency (days per month)	11.06 (4.46)	8.65 (3.50)	10.21 (4.27)
Alcohol typical dose (units)	6.79 (3.71)	5.29 (1.61)	6.26 (3.19)
Alcohol length of use (years)	6.06 (1.95)	4.21 (1.71)	5.41 (2.05)
Cannabis frequency (days per month)	10.87 (9.81)	5.14 (4.91)	8.94 (8.76)
Cannabis monthly use (oz)	0.95 (1.20)	0.70 (0.89)	0.86 (1.10)
Cannabis length of use (years)	3.15 (2.68)	2.44 (1.95)	2.90 (2.45)

***p<0.05** (a)

	Controls		
Aggression, anxiety, depression, age	Male	Female	Total
AQ	72.26 (14.18)	64.46 (16.07)	69.08 (15.33)
Had-A	6.03 (3.65)	7.29 (3.72)	6.54 (3.70)
Had-D	2.91 (2.39)	2.67 (2.33)	2.81 (2.35)
Age	21.23 (1.03)	20.79 (1.14)	21.05 (1.09)
Drug use			
Ecstasy frequency (days per month)	-	-	-
Ecstasy typical dose (tablets)	-	-	-
Ecstasy length of use (years)	-	-	-
Alcohol frequency (days per month)	12.77 (6.44)	10.20 (5.52)	11.73 (6.16)
Alcohol typical dose (units)	8.60 (4.78)	5.71 (2.99)	7.42 (4.36)
Alcohol length of use (years)	5.86 (1.56)	4.79 (1.56)	5.42 (4.63)
Cannabis frequency (days per month)	7.29 (8.44)	5.12 (5.97)	6.41 (7.55)
Cannabis monthly use (oz)	0.69 (0.87)	0.60 (0.90)	0.66 (0.87)
Cannabis length of use (years)	2.79 (2.36)	2.60 (2.16)	2.71 (2.26)

(b)

Table 6.3: Group means (SD) of aggression (AQ), anxiety (Had-A), depression (Had-D) and age, and of frequency, dose, length of use of ecstasy, alcohol and cannabis for (a) ecstasy users and (b) controls in the combined data set

6.4.2(ii) Interpretative Bias Task (Table 3)

Part 1. Sentence processing: A significant group x sentence type interaction [F(1,102)=9.90, p=0.002] and a main effect of sentence type [F(1,102)=11.35, p=0.001] were found, there was no main effect or interactions with gender. As seen in Table 3, controls were faster to complete neutral than potentially aggressive sentences; ecstasy users showed similar reaction times to both. As expected, nearly all of the participants completed all of the sentences correctly. No gender differences were found.

***Part 2. Recognition memory*:** Recognition accuracy showed a main effect of sentence type [F(1,102)=44.10, p<0.0001] indicating that both groups recognised more neutral than aggressive sentences. There were no group differences in recognition, with both groups recognising a similar number of aggressive (ecstasy users 6.06 ±2.55, controls 5.19 ±2.81) and neutral (ecstasy users 7.90 ±1.69, controls 7.95 ±2.06) sentences.

Reaction time to sentences that participants correctly identified as having previously been seen showed a group x sentence type interaction [F(1,102)=6.60, p=0.012]. Ecstasy users were faster than controls at recognising aggressive sentences, while both groups had similar reaction times to neutral sentences (Table 6.3). Confidence ratings for these sentences also showed a group x sentence type interaction [F(1,102)=8.85, p=0.004], indicating that the ecstasy users were more confident in their judgement when recognising aggressive sentences than controls, whereas control participants were more confident than ecstasy users in their recognition of neutral sentences (Table 6.3). There was also a main effect of sentence type [F(1,102)=5.52, p=0.021]. There were no main effects or interactions with gender.

Reaction times for those sentences that participants endorsed as *not* previously seen showed a significant group x sentence type interaction [F(1,102)=8.17, p=0.005], as well as a main effect of sentence type [F(1,102)=8.17, p=0.005]. While control participants showed similar reaction times to both types of sentences, ecstasy users reacted faster to aggressive sentences (Table 6.3). There were no significant group, gender or sentence type differences in the number of sentences participants

incorrectly rejected or in how confident they were in their judgment that they had not seen the sentences previously.

		Part 1: reaction time to completion of sentences	
Ecstasy		**Aggressive**	**Neutral**
	Males	1313.18 (558.74)	1306.85 (543.19)
	Females	1324.15 (409.18)	1260.94 (412.86)
	Total	1317.06 (506.26)	1290.59 (496.84)
Controls	Males	1353.27 (427.00)	1188.41 (370.48)
	Females	1329.27 (460.82)	1144.77 (348.55)
	Total	1343.51 (437.31)	1170.66 (359.31)
		Part 2: response time to sentences endorsed as seen	
Ecstasy Male		3400.61 (1090.2)	3739.35 (1335.94)
	Females	3695.94 (1157.4)	3794.76 (1116.38)
	Total	3505.21 (1111.32)	3758.98 (1250.67)
Controls	Males	4109.14 (1418.95)	3634.17 (1097.92)
	Females	4381.13 (1138.86)	4095.50 (844.50)
	Total	4219.78 (1308.73)	3821.83 (1002.63)
		Part 2: confidence ratings of sentences endorsed as seen	
Ecstasy	Males	3.39 (0.460)	3.35 (0.469)
	Females	3.44 (0.496)	3.38 (0.485)
	Total	3.41 (0.469)	3.37 (0.470)
Controls	Males	3.37 (0.459)	3.57 (0.472)
	Females	3.29 (0.464)	3.48 (0.500)
	Controls	3.34 (0.459)	3.53 (0.481)
		Part 2: response times to sentences endorsed as *not* seen	
Ecstasy	Males	3642.97 (1409.55)	4169.48 (1299.91)
	Females	3637.18 (1130.29)	4342.00 (903.61)
	Total	3640.92 (1305.04)	4230.58 (1167.69)
Controls	Males	4079.69 (1120.43)	4211.00 (1212.88)
	Females	4371.04 (850.95)	4496.63 (936.66)
	Total	4198.20 (1021.71)	4327.19 (1109.18)

Table 6.4: Performance on the cognitive bias task of the 2 combined data sets: group means (SD) of reaction time to sentences completion, response times and confidence ratings of sentences endorsed as seen and reaction times to sentences endorsed as not seen

6.4.2(iii) Self-ratings

As the subjective effects (ARS, BDI, MRS, SES) showed the same pattern of group differences in Curran et al and the new sample reported here, it is not surprising that the combined data set replicated the findings of each data set. Thus, the results are

not reported separately here (see Appendix 8 for descriptive data). The reanalysis with gender showed only one significant difference: the *anxiety* subscale of the MRS showed a day x gender interaction [F(1,102)=5.73, p=0.018] was found showing that females in both groups rated themselves as more anxious than males on day 0. Mean (S.D) for ARS and BDI scores on day 0 and 4 for both male and female ecstasy users and controls are shown in Table 6.4.

	Day 0		Day 4	
	Ecstasy users	Controls	Ecstasy users	Controls
Aggression (ARS)				
Males	21.89 (10.83)	31.28 (14.94)	45.15 (18.62)	30.05 (15.15)
Female	19.47 (10.86)	36.71 (16.07)	40.18 (17.96)	33.67 (17.96)
Total	21.04 (10.79)	33.49 (16.07)	43.39 (17.82)	31.52 (16.30)
Depression (BDI)				
Males	5.35 (4.14)	6.97 (5.22)	11.58 (5.78)	5.31 (4.14)
Females	4.24 (2.91)	8.79 (5.47)	10.18 (3.45)	7.38 (6.05)
Total	4.96 (3.76)	7.71 (5.35)	11.08 (5.09)	6.15 (5.06)

Table 6.5: group means (SD) for self-rated aggression and depression on day 0 and day 4

6.4.2(iv) Pulse rate

A significant group x day interaction was found [F(1,102)=101.82, p<0.0001], with ecstasy users having a much higher pulse rate than controls on day 0 (94.3 ±11.8 vs. 75.1 ±9.6) but similar on day 4 (73.5 ±9.9 vs. 72.5 ±8.7). There was no effect of gender.

6.4.2(v) Correlations

Correlations were carried out separately for males and females to explore the relationship between performance on the interpretative bias task, drug use and self-report measures of aggression. Due to the number of correlations carried out an alpha level of 0.01 was adopted. In female ecstasy users the number of ecstasy tablets taken in a typical session correlated negatively with reaction time of completing both neutral sentences (r=-0.63, p=0.007) and aggressive sentences (r=-0.58, p=0.01) in the first part of the task. No correlations were found between number of ecstasy tablets used on day 0 and any measure of aggression. In female ecstasy users amount of cannabis used per month also correlated negatively with the number of neutral sentences recognised in the second part of the task (r=-0.75,

p=0.001). In male ecstasy users a correlation was also found between units of alcohol consumed in a typical session and the reaction time to neutral sentences recognised in the second part of the task (r=0.48, p=0.007). There were no correlations within the control group.

6.5 Discussion

6.5.1 Part 1 – New data set

The main finding from the analysis of the new data set is that ecstasy users show a bias toward material with an aggressive content when recognising previously ambiguous material 4 days after ecstasy use. Ecstasy users recognised more aggressive sentences than controls, whereas both groups recognised a similar number of neutral sentences. In addition, ecstasy users tended to react more slowly than controls when recognising neutral sentences, while both groups showed similar reaction times to aggressive sentences. There appeared to be an association between frequency of ecstasy use and performance on the task: the more frequently ecstasy was used the fewer neutral sentences were correctly identified. Although bias toward recognition of aggressive material in the sample tested by Curran et al. (2004) manifested itself in reaction times and confidence in recognition, rather than in the number of sentences recognised, both ecstasy using groups demonstrated aggressive cognitive bias using an objective task 4 days after ecstasy use. Thus, both studies showed an association between ecstasy use and performance of the interpretative bias task. That the reaction time effect was not observed in the new sample may reflect various factors, conceivably including the somewhat lower participant number in the present study or other sample variations.

The results on self-rated aggression replicated the findings of three previous studies (Curran et al., 2004; Hoshi et al., 2004; Verheyden et al., 2002), showing that ecstasy users rated themselves as being less aggressive than controls on day 0 and more so on day 4. The results on self-rated depression also replicated three previous studies (Curran et al., 2004; Curran & Travill, 1997; Verheyden et al., 2002), with ecstasy users reporting lower levels of depression than controls on day 0 and higher levels on day 4. Ecstasy users also rated themselves as being less

discontented than controls on day 0 while the opposite pattern of group differences was observed on day 4. These findings and the results from the interpretative bias task, add to the growing body of evidence of increased aggression and a lowering of mood mid-week following weekend ecstasy use. The evidence of increased aggression in ecstasy users found in both the present study and in Curran et al.'s (2004) sample with an indirect, objective measure is important because it is unlikely that the group differences in this task could arise from differences in how ecstasy users and non-users subjectively rate their feelings. Furthermore, although subjective ratings may, in part at least, reflect people's subjective comparisons between the high of the weekend and the tedium of the middle of the working week, it seems improbable that differences on a subtle, objective measure would reflect this.

As the interpretative bias task was only carried out on day 4, it could be argued that pre-existing differences between the groups in aggression lead to the observed pattern of results. However, no group differences were found in trait aggression. Further, when a different information processing task was used to tap aggression, Bond et al. (2004) found no difference between ecstasy users abstinent for 3 weeks and controls. Mid-week lowering of mood is probably a transient phenomenon. Curran et al. (2004) tested participants on the night of drug use, 4 and 7 days later. They found that on day 7 of the study, group differences found on day 4 on subjective rating scales of aggression and depression were no longer present. It is possible, however, that the observed aggression effects reflect a combination of sub-acute effects and neurotoxic effects of long-term MDMA use.

As outlined in the introduction, the bias towards aggressive interpretation of ambiguous sentences and the increased self-rated aggression and depression 4 days following ecstasy use could be related to a serotonergic depletion following the massive release of 5-HT after ingestion of MDMA in ecstasy tablets. However, there are many methodological problems inherent to this type of naturalistic design that may limit the conclusions drawn (see Curran, 2000 and Cole et al., 2002b for reviews). No objective measure, for example urine screening, was used on day 0 to verify use of MDMA. Unfortunately, this was not practical at many of the testing locations, and some participants expressed reluctance to take part if such tests were

used. The ecstasy users did, however, show significantly higher levels than controls on day 0 of many of the known acute physical effects of stimulants, and in addition experienced empathic feelings (e.g. closeness to others, openness to others, euphoria) that are more specifically associated with MDMA use. The groups did not differ on day 4. In addition, they showed a higher pulse rate on day 0 than on day 4 of just over 20 beats per minute faster than controls, paralleling controlled studies administrating MDMA acutely (Mas et al., 1999). Taken together, it seems reasonable to assume that the ecstasy tablets consumed contained MDMA. Although a few of the participants had used alcohol and cannabis several hours before testing on day 4, the amount of drug used was low. However, it may be relevant as there seemed to be some association between years of alcohol use and aggression in the control group. To clarify this issue the data was re-analysed excluding the 7 participants who had used alcohol and/or cannabis of day 4, and it was found the that results were not significantly affected.

6.5.2 Part 1(b) – Combined data set

The main finding of combining our two data sets is that both men *and* women who take ecstasy show a cognitive bias towards material with an aggressive component four days later. While controls were faster at completing neutral sentences than ambiguous aggressive sentences, ecstasy users showed a similar reaction time to both. The ecstasy users were faster than controls at completing possibly aggressive sentences and slower than them at completing neutral sentences. In the second part of the task ecstasy users were faster at recognising aggressive sentences, while both groups showed similar response times to neutral sentences. Ecstasy users were also more confident in their judgements of aggressive sentences than neutral sentences while control participants showed the opposite pattern. In addition, ecstasy users were faster to respond to aggressive sentences they had not previously seen. Overall, this seems to indicate a bias toward material with aggressive content. No gender differences were found in self-rated aggression. Thus, we have found no evidence of gender differences in aggression mid-week following weekend ecstasy use.

Although it was hypothesised that this more objective measure of aggression may pick up subtle gender differences, none were observed. It is possible that gender

differences in aggression vary depending on the measures used. A recent meta-analysis by Knight et al. (2002) found that increased aggression in men was more likely to be found in naturalistic rather than experimental studies of aggression, and furthermore, gender differences were greater for *physical* than for *verbal* aggression. This is also supported by evidence that men are more likely to use direct aggression and women indirect (Bjorkqvist, 1994). In addition, there is evidence of gender differences in responses to anger. Males tend to react with an 'anger-out' or more aggressive behavioural responses, whereas women tend to have an 'anger-in' reaction (Nunn & Thomas, 1999; Newman et al., 1999). Males have been found to be more aggressive when using the Response-choice Aggression Paradigm (Zeichner et al., 1999) in which participants are led to believe they are competing with another on speed of reaction times. Electric shocks are administered to provoke them, and they have the option of giving a range of strength of shocks to their 'partners'. Zeichner et al. (2003) found that not only did men administer more shocks overall, but they also administered shocks earlier in the 'competition' and chose significantly higher intensity of shocks than women. However, Allen et al. (1996) used the Point Subtraction Aggression Paradigm, where aggression is defined by the subtraction of money from an opponent as opposed to being indexed by shock administration. They found no significant gender differences in aggressive responses. These results support the notion that while there may be gender differences in outwardly expressed behavioural aggression, there is little evidence of any gender differences in aggression assessed on other types of measures.

Tryptophan depletion reduces 5-HT function temporarily, and there is little evidence of gender differences in increased aggression following this procedure. The majority of studies investigating aggression following tryptophan depletion in healthy volunteers have been carried out on men (e.g. Bjork et al., 1999; Cleare & Bond, 1995), and most have found increased aggression following the procedure using methods such as the Point Subtraction Paradigm. Two recent studies investigating aggression following tryptophan depletion in women have revealed very similar results to those found with men (Bond et al., 2001; Marsh et al., 2002). Interestingly, there appears to be some evidence that increased aggressive

responding after tryptophan depletion is related to trait aggression (Cleare & Bond, 1995; Dougherty et al., 1999).

From an evolutionary perspective it is advantageous for both males and females to be quick to perceive the potential for aggression in the environment. In other words, an attentional bias toward threat would benefit both genders. However, the behavioural response towards aggressive threat may have conferred evolutionary advantage if differentiated by gender. As Fessler et al. (2004) discuss, it could have been beneficial to males to show physically aggressive responses to other threatening males in order to secure territory and protect females, while for females more low-risk strategies may be better for ensuring survival of themselves and their offspring.

This idea that attentional bias towards aggressive material is a very different construct to outwardly aggressive behaviour, or violence is also supported by the findings of Copello & Tata (1990) who originally used a version of the interpretative bias task. They found that although non-offenders were less responsive to ambiguous aggressive material than offenders, there were no differences between violent and non-violent offenders. Both groups were therefore more aggressive than non-offenders, although one group was more violent (i.e. behaviourally aggressive) than the other. The idea that levels of aggression vary according to the method of measurement used is also supported by the lack of relationship between the subjective and objective measures of aggression employed in the present study.

The methodological problems outlined in part 1(a) equally apply to the combined data set. Also, although over 100 participants were tested the low number of female ecstasy users may have affected the results. An additional problem when investigating gender differences is that phase of menstrual cycle was not controlled for in the present study, and although a recent study found no significant changes in BDI across phases of the menstrual cycle (Symonds et al, 2004), it is possible that hormonal changes do make women more susceptible to changes in mood caused by 5-HT depletion following MDMA use. There are also other factors that can affect 5-HT function that have not been controlled for in any study of mid-week mood in

ecstasy users, including dieting (Cowen et al, 1996) and family psychiatric history (Sobczak et al, 2002).

In conclusion, we have found further evidence that ecstasy users show increased aggressive cognitive bias as well as increased self-rated aggression mid-week following ecstasy use. These findings add to a growing body of evidence that ecstasy users show a change of mood reflected by increased feelings of depression and aggression mid-week following ecstasy use at the weekend. In addition, our results suggest that both men *and* women have an elevated cognitive bias toward aggressive information a few days following ecstasy use. These findings could have further implications. Ecstasy is often portrayed as a benign drug increasing feelings of euphoria and empathy. The opposite effects of dysphoria and aggression, produced by its offset, are likely to have negative interpersonal consequences which may result in increased episodes of confrontation or social isolation. This may perpetuate the desire for the acute calming effects. As people who suffer from depression often also show cognitive impairments (e.g. Brand et al., 1992), the lowing of mood mid-week could also be associated with impaired cognitive function in the many people that take ecstasy regularly.

Chapter 7: Face your fears?

An investigation of the sub-acute, or mid-week, effects of ecstasy on facial expression processing

7.1 Introduction

Serotonin has been implicated in the regulation of social behaviour in both animals (see Borsini et al., 2002), for review) and humans. For example, healthy human volunteers showed increases in assertiveness following repeated l-trytophan administration (Moskowitz et al., 2001). Many psychiatric disorders, including depression and social phobia, are characterized by social and emotional dysfunction, and the majority are effectively treated by selective serotonin reuptake inhibitors (SSRIs).

Harmer et al. (2003a) assert that the recognition of facial expressions is a "crucially important" element of social interaction. The six basic emotions (anger, happiness, sadness, surprise, disgust, fear) are consistently recognised across cultures (Ekman, 1992), and each appear to be modulated by different neural substrates (LeDoux, 2000). While disgust recognition appears to be modulated by the basal ganglia and the insula, fear recognition appears to be associated with the amygdala (see Calder et al., 2001), for review). Manipulation of different neurotransmitters also seems to affect processing of facial expressions differentially (e.g. Blair & Curran, 1999).

In a series of experiments, Harmer and colleagues investigated the role of serotonin in facial expression recognition by pharmacologically manipulating levels of 5-HT. They found that while *increasing* serotonin through either intravenous administration of citalopram (Harmer et al., 2003a) or tryptophan administration (Attenburrow et al., 2003) *improved* recognition of fear in healthy volunteers, *lowering* of 5-HT following tryptophan depletion lead to *impaired* fear recognition (Harmer et al., 2003b). As MDMA's main action is on the serotonergic system it is possible that these experiments model what happens to the human serotonergic system both immediately after and in the days following MDMA administration.

Curran et al. (2004) suggested that the release of 5-HT caused by acute MDMA administration through ecstasy use leads to increased empathy and pro-social behaviour, where as several days later when 5-HT is depleted, the other 'face' of ecstasy is manifested by antipathy and aggression (see section 1.8.1). In light of the findings described above, the current study was designed to investigate the effects of ecstasy use of the recognition of facial expressions. Given evidence relating to the effects of 5-HT manipulation and fear recognition (Attenburrow et al., 2003; (Harmer et al., 2003a; Harmer et al., 2003b) I predict that enhanced 5-HT following acute ecstasy use will improve recognition of fearful facial expressions, and that several days later depletion of 5-HT will lead to impaired fear recognition.

In addition, I expect to replicate the findings of previous studies that demonstrated increases in self-rated aggression and depression several days after ecstasy use (Curran & Travill, 1997; Parrott & Lasky, 1998; Verheyden et al., 2002; Curran et al., 2004).

7.2 Materials and Methods

7.2.1 Design and Participants

An independent group, repeated measures design was used to compare ecstasy users with controls on two test sessions: the night of drug use (day 0) and 4 days later (day 4). Both the ecstasy users and the control participants were recruited in clubs and parties using the snowball sampling technique (Solowij et al., 1992). In this way all participants were recruited from the same social settings and increased the likelihood of matching groups on the use of other drugs. The study was approved by the institutional ethics committee and all participants gave written informed consent both on day 0 and on day 4 (see Appendix 5 for ethics approval and information sheet).

7.2.2 Procedure

On the evening of day 0 participants were taken individually to a quiet room where they were first given an information sheet. If they were willing to participate they were asked for written consent. They then completed the assessments detailed

below. Arrangements were made for the next test session 4 days later, which was generally carried out at the participant's home. Informed consent was obtained once again on day 4, then the day 0 assessments were repeated along with trait measures of mood and a drug use history interview.

7.2.3 Mood assessments (days 0 & 4)

Current mood state was assessed on both days with the following visual analogue scales: Mood Rating Scale (MRS; Bond & Lader, 1974), Aggression Rating Scale (ARS; Bond & Lader, 1986), State Impulsivity Scale (STIMP; Bond & Wingrove, 1997) and a scale of subjective effects which covered common effects of recreational drugs including those specific to MDMA. A modified Beck Depression Inventory (BDI; Beck, 1978) was used to assess how participants had been feeling over the last three days (Curran & Travill, 1997).

7.2.4 Recognition of Facial Expressions (days 0 & 4)

The participants performed the facial expression recognition task on both days of the study. The task used the stimuli from the Facial Expressions of Emotions: Stimuli and Tests (FEEST; Young et al., 2002). There were 30 stimuli featuring a male face showing the six basic emotions - happiness, surprise, sadness, anger, fear and disgust - from the Ekman & Friesen (1976) series (Figure 7.1). These basic emotions are used to create stimuli that are morphed from one emotion to another in 5 stages (10%, 30%, 50%, 70%, 90%). The expressions morphed are anger to happiness, happiness to surprise, surprise to fear, fear to sadness, sadness to disgust and disgust back to anger. All stimuli involved the face JJ (Ekman & Friesen, 1976).

The task was performed on lap top computers and consisted of 6 blocks. In each block, the 30 morphed stimuli were presented in a pseudo-random order. Constraints were in place to ensure that no more than two stimuli with the same majority emotion appeared together. Each stimulus appeared on the screen for 500ms. The task was specially programmed with a response facility whereby the 6 emotions were arranged in an equilateral hexagon in the centre of the right hand side of the screen. This 'hexagon of choice' (Figure 7.2) appeared next to the faces which were presented on the left hand side of the screen.

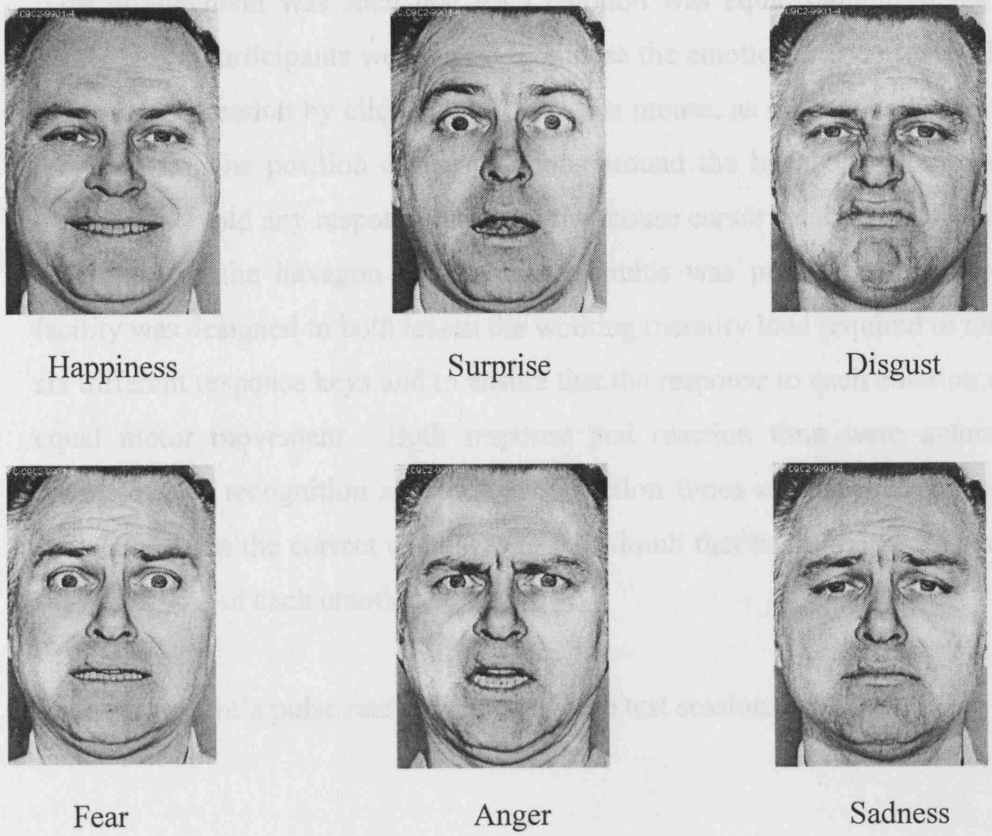


Figure 7.1: Ekman & Friesen's (1976) 6 basic emotions – happiness, surprise, disgust, fear, anger and sadness - showed on JJ, the face used in the facial expression recognition task

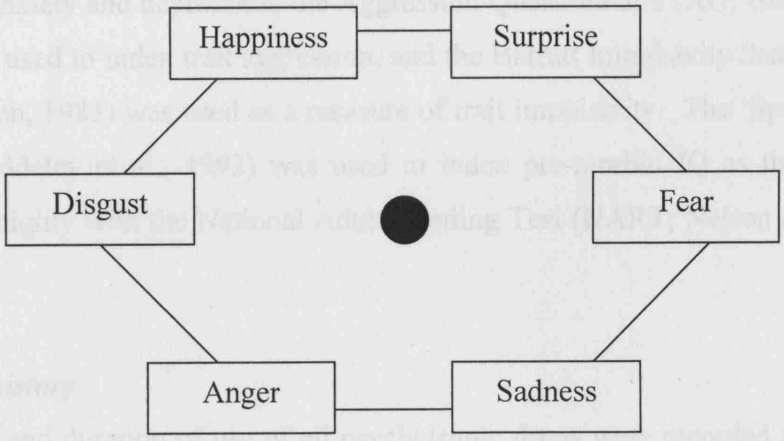


Figure 7.2: the 'hexagon of choice' that appears on the screen along side each stimuli in the facial expression recognition task

This arrangement was such that each emotion was equidistant from the central cursor base. Participants were asked to choose the emotion that corresponded with the facial expression by clicking on it with the mouse, as quickly and accurately as they could. The position of the emotions around the hexagon changed on each occasion to avoid any response bias, and the mouse cursor returned automatically to the centre of the hexagon before each stimulus was presented. This response facility was designed to both lessen the working memory load required to remember six different response keys and to ensure that the response to each emotion required equal motor movement. Both response and reaction time were automatically recorded, and recognition accuracy and reaction times used in the analysis were calculated from the correct responses to the stimuli that had a dominant percentage (90% or 70%) of each emotion.

Each participant's pulse rate was taken at both test sessions.

7.2.5 Additional assessments on day 4

7.2.5(i) Trait measures & pre-morbid IQ

The Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983) was used to index trait anxiety and depression, the Aggression Questionnaire (AQ; Buss & Perry, 1992) was used to index trait aggression, and the Barratt Impulsivity Scale (BS; Barratt & Patton, 1983) was used as a measure of trait impulsivity. The 'Spot the Word' test (Baddeley et al., 1992) was used to index pre-morbid IQ as this measure correlates highly with the National Adult Reading Test (NART; Nelson & O'Connoll, 1978)

7.2.5(ii) Drug use history

Amount, frequency and duration of use of all psychotropic drugs were recorded as well as details of drug use on day 0, 4 and the period between the two days. Demographic information (gender, age, educational background and employment status) was also noted on day 4.

7.3 Statistical analysis

A 2 x 2 repeated measures ANOVA with group (ecstasy versus controls) as a between subjects factor and day (day 0 versus 4) as a within-subjects factor was used on VAS and BDI scores assessed on both days. The 13 variables that make up the ARS showed high internal consistency on both day 0 (Cronbach's $\alpha = 0.88$) and day 4 ($\alpha = 0.90$); the ISRS also showed high internal consistency on both days (day 0, $\alpha = 0.80$, day 4, $\alpha = 0.89$). Thus, a mean aggression and a mean impulsivity score for each participant was used in subsequent analysis. As the subjective effects scale comprises 26 scales, an alpha level of 0.01 was adopted in order to reduce the possibility of type I errors. One-way ANOVAs were used to compare groups in use of alcohol, cannabis and cocaine, apart from the comparison of years of cannabis use, years of cocaine use and amount of cocaine used on day 0 where a Mann-Whitney U test was used due to non-parametric data. A 2 x 2 x 6 repeated measures ANOVA was used to analyse the facial expression recognition task, with group (ecstasy versus controls) as a between subject factor, and emotion (happiness, surprise, sadness, anger, fear and disgust) and day (day 0 versus 4) as within-subjects factors. As the assumptions of sphericity were violated, a Greenhouse-Geisser correction was used. The data from 2 participants in the ecstasy group was not analysed due to computer failure on day 0. As a significant gender differences was found between the groups (see demographics), gender was used as a covariate throughout the analyses. The relationship between recognition of fearful facial expressions and ecstasy use was explored using Pearson product-moment correlations. All data were analysed using SPSS for Windows versions 11.0.

7.4 Results

7.4.1 Demographics

There were 37 participants aged between 20 and 32 years old; 16 ecstasy users (10 males, 6 females) and 21 controls (6 males, 15 females). There was a significant difference between the number of males and females in each group ($\chi^2 = 4.26$, $p = 0.039$). Due to this imbalance, gender was used as a covariate throughout the analyses. There were no group differences in age, pre-morbid IQ (Spot the Word),

trait aggression (AQ), impulsivity (BS), anxiety or depression (HADS) (Table 7.1). All but 2 participants in the control group were either undergraduate students or graduates in full time employment.

	Ecstasy users	**Controls**
Age	21.94 (2.98)	20.95 (2.11)
Spot the Word	46.38 (4.00)	48.05 (4.03)
AQ	68.50 (12.05)	67.62 (14.61)
BS	55.06 (12.35)	53.90 (15.72)
HADS-D	3.06 (1.88)	2.57 (2.20)
HADS -A	7.06 (1.88)	6.95 (3.60)
Alcohol frequency (days per month)	14.75 (7.36)	11.86 (6.79)
Alcohol typical dose (units per session)	7.81 (2.37)	9.10 (3.71)
Alcohol length of use (years	6.75 (3.04)	5.57 (1.60)
Cannabis frequency (days per month)	4.56 (5.09)	4.29 (8.41)
Cannabis typical dose ('joints')	1.03 (1.16)	0.52 (1.36)
Cannabis length of use (years)	3.19 (4.25)	0.88 (1.84)
Cocaine frequency (days per month)	**2.06 (1.88)***	**0.86 (1.46)**
Cocaine typical dose ('lines')	4.31 (4.45)	1.90 (3.95)
Cocaine length of use (years)	**2.00 (2.07)***	**0.62 (1.07)**

***p<0.05**

Table 7.1 Group means (SD) for age, Spot the Word test, Aggression Questionnaire (AQ) score, Barratt Impulsivity Scale (BS) score, HADS-D (depression), HADS-A (anxiety) and measures of alcohol and cannabis use.

In the ecstasy group, participants reported using ecstasy for an average of 3.31 (2.18) years. They took ecstasy on an average of 2.63 (1.41) days in a typical month, taking 2.25 (1.05) tablets in a typical session. Seven of the control group had previously tried ecstasy, but none were regular users. They did, however, regularly use other recreational drugs such as cannabis. There were no group differences in measures of either alcohol or cannabis use (Table 7.1). However, two measures of cocaine use differed significantly between the groups: ecstasy users had moreyears of use ($U = 101.50$, $p = 0.024$, two-tailed) and frequency of use [$F(1,35) = 4.84$, $p=0.035$). Reported regular (>1 day per month) use of other drugs included amphetamines (one ecstasy user) and ketamine (two ecstasy users).

	Ecstasy users			***Controls***		
	Before	After	Total	Before	After	Total
Ecstasy (tablets)	2.72 (1.08)	0.34 (0.60)	3.06 (1.12)	0.00	0.00	0.00
Alcohol (units)	10.88 (5.97)	1.69 (2.30)	12.56 (6.12)	10.71 (3.87)	2.00 (2.30)	12.71 (4.37)
Cannabis ('joints')	0.00	0.19 (0.54)	0.19 (0.54)	0.45 (1.47)	0.14 (0.36)	0.60 (1.53)
Cocaine ('lines')	0.81 (1.05)	0.56 (0.95)**	1.38 (1.30)**	0.19 (0.87)	0.00	0.79 (0.87)

****significant at p<0.01**

Table 7.2 Means (SD) of ecstasy, alcohol and cannabis use before testing, after testing and total on day 0

On day 0, the ecstasy users took an average of 3.06 (1.12) ecstasy tablets (Table 7.2). All the participants had drunk alcohol; 2 ecstasy users and 3 controls had smoked cannabis. There were no significant differences in quantities of alcohol and cannabis consumed on day 0 (Table 7.2). Only 1 control had used cocaine, compared to 10 ecstasy users, and there was a significant difference in the number of 'lines' of cocaine used ($U = 75.50$, $p < 0.01$, two-tailed). Between the two test sessions 5 ecstasy users had smoked cannabis and 12 ecstasy users and 10 controls had drunk alcohol. In addition, 2 ecstasy users and 2 controls had drunk between 2 and 4 units alcohol prior to testing on day 4.

	Day 0		***Day 4***	
	Ecstasy users	Controls	Ecstasy users	Controls
Happiness	85.7 (21.35)	89.3 (13.86)	96.1 (5.53)	94.4 (8.78)
Surprise	72.0 (20.57)	76.2 (16.83)	81.5 (6.88)	74.6 (13.62)
Sadness	61.0 (25.77)	63.7 (23.28)	78.0 (11.14)	72.6 (17.56)
Anger	41.7 (23.80)	33.9 (25.56)	70.5 (15.63)	56.3 (28.19)
Fear	50.6 (23.68)	43.8 (22.23)	54.5 (20.64)	63.9 (20.34)
Disgust	64.6 (23.67)	61.3 (29.00)	63.4 (19.14)	72.4 (20.69)

Table 7.3: Percentage (SD) correct for each emotion of day 0 and day 4

7.4.2 Recognition of facial expressions

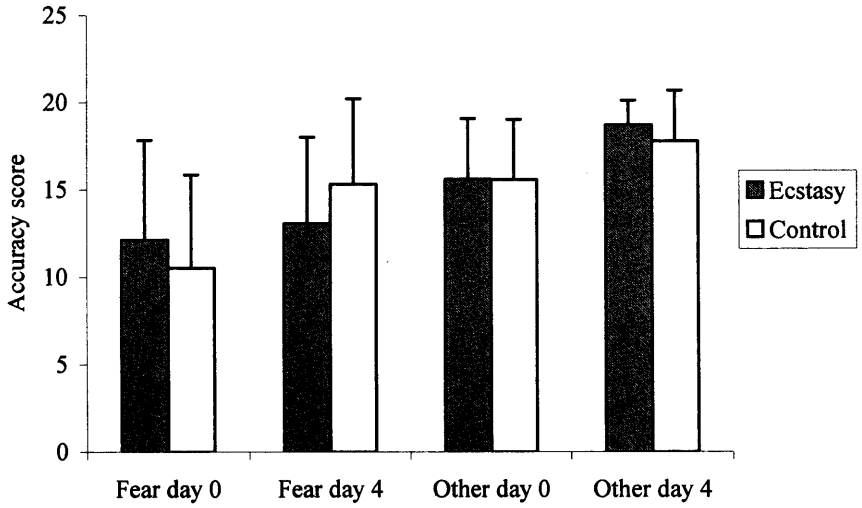


Figure 7.3: Accuracy of recognition of fearful facial expressions compared to all other emotions by ecstasy users and controls on day 0 and 4

A significant emotion x day x group interaction was found for accuracy [$F(5,160)=3.260$, $p=0.019$], as well as significant main effects of emotion [$F(5,160)=14.875$, $p<0.0001$] and day [$F(1,32)=13.193$, $p=0.001$] (Table 7.3). Repeated measures ANOVAs with day as a within subjects variable, group as the between subjects variable and gender as a covariate were carried out for each emotion separately. Trends towards significant day x group interactions were found for fear [$F(1,32)=3.185$, $p=0.084$] and disgust [$F(1,32)=3.517$, $p=0.07$]. Disgust also showed a significant day x gender interaction [$F=1,32=4.696$, $p=0.038$] and a main effect of day [$F=1,32)=5.474$, $p=0.026$]. No emotion x gender interactions were found. No simple effects were found when comparing groups on each individual emotion on each day separately. As the hypothesised difference was expected on recognition of fear, and trends toward significant interactions were found for fear and disgust, recognition data for these two emotions were individually compared to the mean accuracy of all the other 5 emotions. Comparing fear to all other emotions yielded a significant emotion x day x group interaction [$F(1,32)=4.293$, $p=0.046$], a significant main effect of emotion [$F(1,32)=13.938$, $p=0.001$] and of day [$F(1,32)=9.898$, $p=0.004$]. The ecstasy users were more accurate than controls at recognising fear on day 0 and less accurate than controls at recognising fear on day 4 (Figure 7.3), although no significant posthoc differences

were found. The groups did not differ in the mean recognition of the other 5 emotions. No significant interactions were found when comparing disgust to all other emotions. No significant interactions or main effects were found for the analysis of reaction time.

7.4.3 Self-rated scales

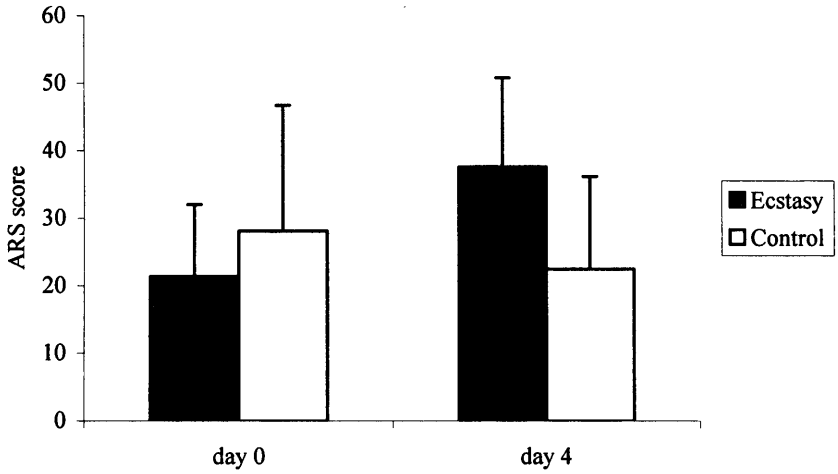


Figure 7.4: Mean aggression scores on day 0 & 4 for the ecstasy and control groups

Aggression rating scale (ARS): A significant group x day interaction was found on state aggression ratings [F(1,34)=14.164, p=0.001]. Ecstasy users' ratings were lower than controls on day 0 but higher than controls on day 4 (Figure 7.4). There were no significant gender effects.

Mood Rating Scale (MRS): The MRS yields three factors: sedation, discontentedness and anxiety. A group x day interaction was found for alert/sedated [F(1,34)=12.516, p=0.001] showing that ecstasy users were less sedated than controls on day 0 and more sedated than controls on day 4 (Table 7.4). There was no main effect of group or day. A significant day x group interaction was found for contented/discontented [F(1,34)=4.866, p=0.034, as well as a day x gender interaction [F(1,34)=5.377, p=0.027]. In both groups males were less contented that females on day 0 and more contented on day 4. The calm/anxious scale showed no significant interactions or main effects (Table 7.4).

Beck Depression Inventory (BDI): There were no significant interactions or main effects on BDI scores (Table 7.4).

Impulsivity Self Rating Scale: A significant group x day interaction was found on state impulsivity self-ratings [F(1,34)=5.671, p=0.023]. Although the ecstasy users' ratings were similar on both test days, the controls scored higher than the ecstasy group on day 0 and relatively lower on day 4 (Table 7.4). There were no significant gender effects.

	Ecstasy users		***Controls***	
	Day 0	Day 4	Day 0	Day 4
MRS - sedation	37.92 (18.13)	45.28 (15.35)	50.38 (14.31)	34.89 (15.14)
MRS - discontentedness	19.26 (12.42)	36.20 (14.59)	24.82 (13.58)	30.79 (18.25)
MRS - anxiety	35.50 (23.28)	30.09 (11.52)	40.60 (21.00)	27.23 (19.40)
BDI	4.88 (3.58)	5.94 (3.17)	5.52 (5.93)	4.81 (3.89)
ISRS	51.90 (16.72)	52.63 (16.30)	58.93 (14.99)	43.69 (19.16)
Pulse rate	99.14 (14.80)	72.86 (8.07)	79.81 (8.02)	71.24 (6.56)
Teeth grinding	43.75 (28.25)	8.09 (14.77)	14.31 (23.07)	11.24 (19.91)
Jaw clenching	46.81 (29.48)	8.63 (17.16)	11.62 (18.49)	8.40 (13.65)
Dry mouth	57.03 (29.07)	21.69 (26.12)	29.98 (25.91)	18.31 (23.98)
Energy	59.28 (31.31)	35.25 (15.70)	42.64 (28.32)	44.45 (22.70)
Euphoria	67.31 (16.53)	19.34 (15.76)	44.67 (27.89)	15.19 (15.94)
Open to others	72.31 (14.54)	37.56 (18.65)	59.57 (27.65)	43.76 (19.19)

Table 7.4: Group means (SD) on days 0 and 4 for the Aggression rating scale (ARS), mood rating scale factors, Beck Depression Inventory (BDI), Impulsivity Self Rating Scale (ISRS), pulse rate and subjective effects scales.

Subjective effects scale (SES): At $p<0.01$ level, 4 of the scales showed a significant group x day interaction: energy [F(1,34)=8.852, p=0.005], euphoria [F(1,34)=9.209, p=0.005] teeth grinding [F(1,34)=11.829, p=0.002] and jaw clenching [F(1,34)=15.470, p<0.0001], with ecstasy users showing higher ratings than controls on day 0, but similar levels on day 4. In addition, 2 scales showed a

significant day x gender interaction: anxiety [F(1,34)=9.642, p=0.004] and agitated [F(1,34)=12.866, p=0.001]. In both cases male participants scored higher than female participants on day 0, and lower on day 4. There were 2 scales that showed trends towards significant day x group interactions: dry mouth [F(1,34)=5.064, p=0.031] and openness to others [F(1,34)=5.049, p=0.031]. In these two cases, ecstasy users scored higher on the scales than controls on day 0 and were similar on day 4 (Table 7.4).

7.4.4 Pulse rate

Two participants in the ecstasy group did not have their pulse taken on day 0, thus their pulse data on day 4 was also excluded. A significant group x day interaction [F(1,32)=22.072, p<0.0001] as well as a significant main effect of both day [F(1,32)=65.876, p<0.0001] and group [F(1,32)=11.622, p=0.002] reflected higher pulse rates in ecstasy users compared to controls only on day 0 (Table 7.4). There were no significant gender interactions.

7.4.5 Correlations

Accuracy of fear recognition and self-rated aggression were correlated with self-reported ecstasy use. Within the ecstasy group, accuracy of fear recognition on day 4 was negatively correlated with both years of ecstasy use (r=-0.54, p=0.048) and number ecstasy tablets taken on a typical session (r=-0.58, p=0.031). As the groups differed significantly on cocaine use on the night, this measure was also correlated with fear recognition on day 0 (r=-0.306, p=0.287) and day 4 (r=-0.015, p=0.959), but no significant correlations emerged. Significant correlations were found between years of cocaine use and ecstasy use (r=0.83, p<0.001) and the number of days that cocaine and ecstasy were used in a typical month (r=0.67, p=0.005).

7.5 Discussion

As predicted by the original hypothesis, there was some evidence that participants in the ecstasy-using group recognised a greater number of fearful facial expressions than controls following acute ecstasy use, but four days later, the reverse was found with ecstasy users recognising fewer fearful facial expressions than controls.

The effect on fear recognition found in this study was subtle, emerging as a group and day interaction with fear versus all other emotions. The subtlety of this effect may derive from the relatively small number of participants and/or the gender imbalance across groups. However, the results are in accord with the findings of Harmer and colleagues that increasing 5-HT release enhances recognition of fearful facial expressions (Attenburrow et al, 2003; Harmer et al., 2003a) and decreasing 5-HT release impairs their ability to recognise fearful facial expressions (Harmer et al., 2003b).

These findings could be attributed to the serotonergic changes caused by MDMA use, whereby on day 0 the efflux of stored 5-HT enhanced the recognition of fearful facial expressions. On the other hand, the ecstasy users' impairment in recognition accuracy on day 4 accords with the notion of depleted 5-HT following MDMA use and suggests a reciprocal role for 5-HT in the processing of fear relevant cues.

There were no significant group differences in reaction times to correctly recognise fearful facial expressions. Thus, changes in accuracy in recognising fearful expressions was not a by-product of any speed-accuracy trade off that might be influenced by the stimulant effects of MDMA on the night of use. Practice effects could also make the results difficult to interpret. Controls showed an improvement of 20.1% in fear recognition from day 0 to day 4, which may largely reflect practice effect on the task. However, the ecstasy users' fear recognition increased by only 3.9%. That the change in ecstasy users appears subtle probably reflects a more substantial relative decline if practice effects are taken into account. Practice effects also emerged on happiness, sadness and anger. For all these emotions the increase in accuracy of recognition by ecstasy users from day 0 to day 4 was markedly greater than that for fear.

Fear is thought to be the most difficult expression to recognise (Ekman & Friesen, 1976), and it has been argued that seemingly selective impairments in fear recognition in patients with lesions is more a reflection of task difficulty (Rapcsak et al., 2000).

It could be argued that our findings arise from impaired learning following acute ecstasy use. However, there is as yet no evidence to suggest that acute MDMA administration impairs learning. In fact, augmentation of serotonin through acute citalopram administration has been found to improve memory consolidation in healthy volunteers (Harmer et al., 2002) and, as MDMA administration also leads to increased levels of 5-HT available, there seems no reason to assume that MDMA should cause impaired learning. On the other hand, there is evidence that ecstasy users off-drug have memory impairments compared to controls. However, as the ecstasy users improved on four out of the six emotions it is unlikely that either memory impairments or impaired learning caused by MDMA administration account for the results observed.

The present findings are consistent with the view that 5-HT plays a wider role in fear-related processes. Several studies have found that serotonergic input to the amygdala plays an important role in conditioning and fear responses in humans and animals (for review see Davis & Whalen, 2001). The amygdala has also been implicated in the processing of fearful facial expressions. Patients with amygdala damage show deficits in fear recognition independent of other expression such as anger (Sprengelmeyer et al., 1999) and masked presentations of fearful facial expressions illicit increased blood oxygen level-dependant fMRI signal in the amygdala, even when fear processing is implicit and participants report only seeing neutral faces (Whalen et al., 1998).

Two indices of ecstasy use - the number of years ecstasy has been used and the amount of tablets taken on day 0 - correlated negatively with the participants' ability to recognise fearful faces on day 4. Thus, the greater the number of ecstasy tablets taken on day 0 the worse the participants' fear recognition accuracy on day 4. Similarly, the longer they had been using ecstasy, the worse their day 4 fear recognition accuracy score. These two correlations are clearly interrelated. As with most centrally acting drugs, tolerance to ecstasy's effects builds up over repeated use so that users generally increase the dose taken over time to attain the same effect (Verheyden et al., 2003a; Parrott, 2005). Thus, longer use of a drug is associated with a higher dose per drug using session. Higher dosage on day 0 would, in theory, lead to greater depletion of 5-HT mid-week, and in accordance

with the hypothesis that depleted 5-HT leads to impairments in fear recognition, higher dose on day 0 would translate to greater impairment on day 4.

Scores on self-rated aggression (ARS) replicated the results of 3 previous studies (Verheyden et al., 2002; Curran et al., 2004; Hoshi et al., 2006) in that ecstasy users scored lower than controls on day 0 and higher on day 4. As no significant difference was found between the groups on a trait measure of aggression (AQ), this suggests that mid-week increase in aggression is a transient phenomena related to depletion of 5-HT following acute MDMA use. This idea is supported by literature that suggests that low levels of 5-HT are associated with increased aggression (Cleare & Bond, 1997) and that increases in 5-HT, through administration of SSRIs, leads to increases in positive affiliate behaviour (Tse & Bond, 2002).

Unlike the findings of several previous studies (Curran & Travill, 1997; Parrott & Lasky, 1998; Verheyden et al., 2002; Curran et al., 2004), no significant differences were found in depression (BDI). However, the pattern of group means was in the same direction as previous studies. The gender imbalance of the groups may have affected the present results, as female users have been shown to be more vulnerable to low mood following MDMA use and female participants were in a minority in the present study's ecstasy using group (Verheyden at al., 2002).

As with virtually any naturalistic investigation of recreational drug users, there are methodological considerations that limit the conclusions of this study (see section 1.8.2). Although the groups were well matched on pre-morbid IQ, age, trait aggression, depression, impulsivity and anxiety, as well as use of cannabis and alcohol, the dose or purity of MDMA taken is unknown. However, ecstasy users in the present study reported many of the 'trademark' acute effects, such as teeth grinding and jaw clenching, that have been found in lab-based studies of acute administration of MDMA (Harris et al., 2002; Vollenweider et al., 1998) and their pulse rate was significantly higher on day 0, another factor that indicates stimulant consumption (Mas et al, 1999). Although hair and urine analysis could have been used to objectively confirm drug use on the night of the study, it would have been

impractical given the setting of the study. Self-reported drug use histories are also problematic due to their unreliability (Cooper et al., 2000).

Both lifetime indices of cocaine use (frequency and years of use) and amount of the drug used on day 0 differed significantly between the groups. There were, however, no correlations between cocaine use and either fear recognition or self-reported aggression. There was also a gender imbalance between the groups in the present study with more males in the ecstasy group. This could be of particular importance as 2 out of the 3 studies by Harmer and colleagues used only female participants (Attenburrow at al, 2003; Harmer et al., 2003a) and the other found decreased recognition of fear following tryptophan depletion in female but not male participants (Harmer et al., 2003b). However, covarying gender in the present study did not affect the pattern of significant results. There is evidence that females are more accurate at recognising facial expressions (Thayer & Johnsen, 2000), and evidence from functional magnetic resonance imaging indicates the possibility of gender differences in the neural correlates of facial expression recognition (Lee et al., 2002). In addition, previous literature suggests there may be gender differences in the acute, residual and long-term effects of MDMA (see section 1.10). Therefore, it would be important to carry out a future study with a larger sample of female ecstasy users to explore these issues.

Interestingly, both groups showed the greatest improvement in recognition for anger, with both groups recognising over 20% more on day 4. The results relating to anger could be related to the amount of alcohol consumed on day 0. Borrill et al. (1987) found that alcohol was associated with greater impairments of judgments of anger than of other emotions, and both groups in the present study had consumed a large amount of alcohol (a mean of over 10 units) before carrying out the task on day 0.

It is tempting to speculate that heightened awareness of facial expression recognition in ecstasy users is a component of the acute subjective effect of increased empathy unique to MDMA. However, there is no *a priori* reason why increased empathy should be reflected in increased accuracy to recognise only the single emotional expression of fear and not any of the other basic emotions.

In summary, results from the present study indicate that an acute dose of MDMA may subtly affect the recognition of fearful facial expressions. These results compliment previous findings that suggest that the recognition of fear is modulated by serotonin. Further, the differences in the processing of fearful facial expressions occurred alongside increases in aggression mid-week following weekend ecstasy use. The fact that ecstasy users are subtlety misinterpreting forms of social cues and are susceptible to negative feelings several days after taking the drug has implications for the functioning and well-being of recreational ecstasy users.

Chapter 8: General discussion

"It is good to have an end to journey towards, but it is the journey that matters in the end" *Ursula LeGuin*

As outlined in section 1.12, this thesis was intended to address 2 main research questions:

1) What are the long-term effects of ecstasy use?
2) What are the sub-acute, or mid-week, effects of ecstasy use?

In this chapter I will briefly summarise the findings from the studies reported and assess how they answer these questions. I will also discuss the relevance of these findings to the wider body of ecstasy research, and attempt to outline the shortcomings and possible future directions of both my own research and the field as a whole.

8.1 What are the long-term effects of ecstasy use?

8.1.2 Long-term effects of ecstasy use on cognitive function and aggression

As reported in Chapter 4, I assessed the long-term effects of ecstasy use on cognitive function by administering a battery of cognitive tests to current ecstasy users, ex-ecstasy users, a matched poly-drug control group and a drug-naïve control group. In summary, there was an overall tendency for impaired verbal learning and memory in the drug using groups, particularly the current ecstasy users. There was also evidence of reduced response inhibition in the current ecstasy users and the poly-drug control group, and some evidence of slowed planning speed in ex-ecstasy users. The findings relating to learning and memory support previous research finding impairments in drug users, irrespective of whether they use ecstasy or not. Results indicating that the ex-ecstasy users show less memory impairment and greater response inhibition than the current ecstasy users and the poly-drug controls indicates that there maybe some recovery: that impairment could be related to

current drug use rather than being a long-lasting effect of it. The importance of matching groups for both recency of drug use and mood traits was highlighted as the majority of these group differences were no longer apparent after controlling for these factors.

Much of the research in to the long-term effects of ecstasy has focussed on its effects on cognitive function, and this focus has primarily been explained by the link between cognitive function and serotonin. However, as discussed in section 1.5.4, this link is far from clear. In fact, other neurotransmitters have been shown to have a clearer link with cognitive function. For example, there is far more consistent evidence that cholinergic mechanisms modulate learning and memory (see Gold, 2003), for review). Glutamatergic and GABAergic drugs, as well as THC, have also been repeatedly implicated in memory function (see Curran & Weingartner, 2002), and there is evidence of dopaminergic involvement in working memory (e.g. Mehta et al., 2005). In many of the studies in which authors have related cognitive function to serotonergic neurotoxicity, no actual measure of 5-HT function has been used to attempt to confirm this speculative relationship. Clearly the relationship is not as simple as described as previous research has found evidence of cognitive impairments in abstinent ecstasy users who show no differences in serotonergic function (e.g. transporter density, Thomasius et al., 2003).

The rationale for linking serotonin and mood is based on firmer evidence. This is especially true for the serotonin/depression link which, as discussed in section 1.5.1, has been demonstrated by evidence such as the efficacy of SSRIs, relapse of depressed symptoms following tryptophan depletion and blunted responses to serotonergic neuroendocrine challenges in depressed patients. Although the basis for the serotonin/aggression link appears less robust in comparison to the depression literature, (see section 1.5.2), there is still a convincing amount of literature supporting the link, including evidence of successful treatment of aggression with SSRIs (see Bond, 2005, for review).

In Chapter 5, an interpretative bias task was used to assess aggression in the groups outlined above using an information processing paradigm. There were no group

differences in cognitive bias toward material with an aggressive content. These results add to the body of knowledge suggesting that increased aggression found in ecstasy users several days after taking the drug is a transient rather than a persisting effect.

8.1.3 Why are results inconsistent?

Overall there were very few differences between the four groups investigated, indicating no strong evidence of cognitive impairment or increased aggression in either current or ex-ecstasy users. Although this may seem contradictory to the majority of previous studies, in reality the results from the large body of research into the long-term effects of ecstasy use are overall equivocal, and I believe it is necessary to attempt to understand why consistent findings have not been achieved in this field. Methodological problems endemic to one-off cross-sectional investigations have been discussed at length throughout this thesis and will not be repeated in detail here. The following will add to previous discussions in relation to methodological problems contributing to the inconsistency of findings in the field.

8.1.3(i) Poly-drug use among ecstasy users

The vast majority of ecstasy users take other recreational drugs, and this was the case with the ecstasy users tested throughout this thesis, highlighting the importance of matching a control group for the use of other drugs. The poly-drug groups assessed in this thesis are relatively unique in that they matched both current and ex-ecstasy using groups in terms of the use of *all* other recreational drugs unlike many previous studies that match well only for cannabis and alcohol use. The difficulty I experienced recruiting this group highlights and interesting phenomena: very few people use drugs such as cocaine, amphetamines or LSD without having also used ecstasy.

Approximately 2000 people were screened in order to find suitable participants for this thesis, and many came from English speaking countries outside the UK, including Australia and South Africa, where recreational ecstasy use started later. As other drugs used by ecstasy users, including cannabis, cocaine, amphetamines and ketamine have been linked to cognitive impairment after long-term use (Block et al., 2002; Bolla et al., 1998a; Morgan et al., 2004; Solowij et al., 2002), it is

clearly essential to match for them when attempting to investigate the cognitive effects of ecstasy use.

However, although poly-drug use was well matched for in the studies presented in this thesis, it is important to note here that poly-drug use can never be truly controlled for as it is unlikely that taking these drugs in combination has the same effects as taking them alone: matching for poly-drug use does not account for the interactions of MDMA with other substances. Although it is possible to match for years of use, frequency and amount of various drugs used, this does not cover the myriad of other factors which are important in drug interactions. These include timing of ingestion of each drug relative to the others, individual differences in tolerance and sensitivity to each drug, and individual variations in pharmacokinetic processes such as metabolism. For example, Clemens et al. (2004) found that co-administration of methamphetamine increased MDMA–induced serotonergic neurotoxicity in rats. Similar results have been reported after co-administration of amphetamines (O'Loinsigh et al., 2000). As discussed in section 1.9, there has been some evidence that cannabis use could be neuroprotective when used in combination with MDMA in rats, and similar evidence has been found with alcohol co-administration (Johnson et al., 2004). It is possible that similar effects are found in humans, and that other drugs used in combination could either exacerbate or ameliorate the effects of MDMA use. These interactions could go some way in explaining the variation in results across studies of the long-term consequences of ecstasy use.

8.3.1(ii) Pre-morbid differences

Another likely candidate for the inconsistency of findings in this field is pre-morbid differences between groups and individuals. There is no way of controlling for these types of differences in cross-sectional designs, and they may influence results in a variety of ways. Many differences in psychopathology, such as increased aggression and depression, that have previously been attributed to ecstasy use (see sections 1.8.9 i & ii) may be pre-existing and may in fact have lead to an increased likelihood of using ecstasy. However, de Win et al. (2006) recently conducted a prospective study initially assessing 188 ecstasy-naïve participants, 59 of whom later started taking ecstasy. They concluded that prior levels of depression,

impulsivity and sensation-seeking did not predict later ecstasy use. Interestingly, in this sample ecstasy use did not increase levels of depression or impulsivity, although as may be expected, there was some evidence it did increase levels of sensation seeking. Many authors have explained observed cognitive impairments as a result of MDMA-induced serotonergic dysfunction following ecstasy use when it is possible that they predated ecstasy use. In addition, many studies report higher levels of depression in ecstasy users than I found in Chapter 4. As an established link exists between depression and cognitive function, this could also be a factor contributing to the lack of significant differences in Chapters 4 & 5. Even studies finding differences in serotonergic function in ecstasy users could, in fact, have identified pre-existing differences. An intriguing idea that could also be relevant to the variation in results is that pre-existing genetic variations could lead to differences in susceptibility to cognitive deficits and increased psychopathology following ecstasy use (see sections 4.5 & 5.5).

8.1.3(iii) Historical aspects

An aspect of ecstasy use which is often ignored is its place in a sub-culture that is, like any other sub-culture, changing over time. Variations in results of studies into the "effects of" ecstasy use may in some respects reflect this. When ecstasy first came to the UK, people very rarely took it if they were not at a rave or a dance party. By the late nineties, dance music was extremely popular, and while the majority of large-scale raves had been stopped by the Criminal Justice & Public Order Act (1994), most clubs played dance music. Although there is little research into this, I believe that many more people now attended clubs and *do not* take ecstasy. These people spend time in the same environment as ecstasy users have always done, and will experience fatigue caused by prolonged periods of dancing, and sleep deprivation in the same way. As discussed by Cole et al. (2002b), these factors can also affect cognitive performance. At the same time, ecstasy users started to take the drug in much more varied settings, such as at house parties and in pubs. In this way both the control participants and the ecstasy using participants volunteering for research have changed as the use of the ecstasy has become less synonymous with clubbing. The environment that the drug is used in could be related to its effects. For example, Parrott (2004b) discusses the possibility that evidence of increased MDMA-induced neurotoxicity in rats housed in hot and

overcrowded environments could have implications of humans taking ecstasy at raves. The overall trend towards less consistent findings of cognitive impairments in ecstasy users could reflect fewer users taking the drug in environments that could exacerbate negative effects. This suggestion is, of course, purely speculative, and in fact recent research indicates that body temperature increases in humans following MDMA administration regardless of ambient temperature (Freedman et al., 2005). However, as this study was carried out in a laboratory, it cannot account for the possible interactions of this observed increase in temperature and the effects of prolonged exercise and overcrowding experienced at raves.

Another interesting finding from this thesis was that the current user group tested took ecstasy more frequently and took more tablets per session than the ex-users, precisely the reverse of the pattern found in previous studies (e.g. Curran & Verheyden, 2003). This could indicate a change in the patterns of ecstasy use: that people in recent years are taking more of the drug. This could reflect the drop in price, with ecstasy tablets now available for as little as £2 in parts of the UK compared to £15 in the late eighties. If this is the case it would be logical to expect greater impairments, although as several of the more recent, well controlled studies have not found evidence of impairment in ecstasy users, the literature does not support this.

The pattern of which drugs are used conjointly with ecstasy has also changed recently. Simply by looking at the ecstasy users volunteering for the research presented in this thesis, a significant increase can be seen in the numbers also regularly ($\geq$1 day per month) taking cocaine and ketamine in just 3 years (see Figure 8.1). Ketamine is an NMDA-receptor agonist which blocks long-term potentiation (LTP), the mechanism which leads to changes in strength of synaptic connections and which is thought to underpin memory. The data also shows that the percentage of participants having ever *tried* ketamine has increased from 51% to 88% in the last 2 years, perhaps an indication that in future even more ecstasy users will use ketamine on a regular basis. These findings are supported by recent government research indicating an increase in the use of both cocaine and ketamine, while ecstasy use has shown a slight decline. In future the effects of the recreational use of these drugs may merit more research.

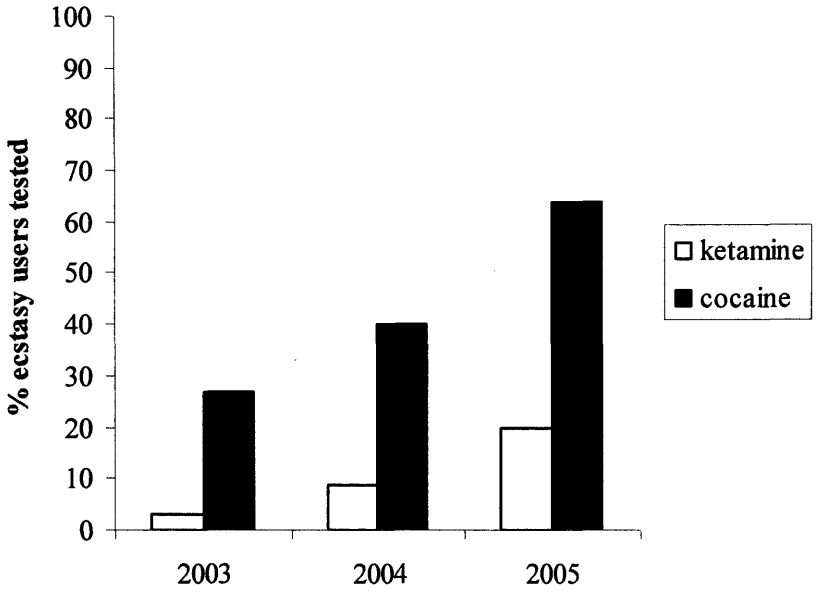


Figure 8.1: Percentage of current ecstasy users tested for this thesis reporting regular use of cocaine and ketamine in 2003, 2004 & 2005.

A major problem with much research is lack of information about the amount of MDMA ingested in ecstasy tablets. The pattern of increased use may reflect a drop in the amount of MDMA in ecstasy tablets. Cole et al. (2002a) comment that while ecstasy tablets contained 90-120mg of MDMA between 1991 and 1995, this fell to 73-88 mg in 1996-2001. It is possible that these average amounts have fallen again more recently. Parrott (2004a) also discusses the implications to research of the variations over time of the proportion of ecstasy tablets that contain MDMA. Although these historical changes in the patterns of ecstasy use are often over looked, it is important not to ignore these and other more 'social' aspects of ecstasy use when considering the contradictory nature of the research to date.

8.1.4 Long-term effects of ecstasy use on dopamine and serotonin

In Chapter 2, pre-synaptic dopaminergic function was investigated using positron emission tomography (PET) with the ^{18}F-dopa ligand. The results showed that ecstasy users abstinent for at least 1 year had higher ^{18}F-dopa uptake in the putamen than drug-naïve controls, which could suggest a long-lasting dopaminergic effect caused by ecstasy use. The main difficulty with interpretation of these findings is that we cannot specify the underlying mechanisms responsible for increased ^{18}F-

dopa uptake. On the one hand, increased AADC activity could be a primary cause, suggesting increased dopamine synthesis as in the case of schizophrenics. On the other hand, it could be a secondary response to reductions in extracelluar dopamine which in turn could be related to changes in other functional units of the dopaminergic system. For example, as seen in pre-symptomatic Parkinson's, the observed increase in ^{18}F-dopa could imply a compensatory mechanism whereby reduction of dopamine transporters leads to upregulation of decarboxylase activity in order to maintain dopamine levels. If these changes are compensatory in nature, the consequences may only become apparent during the natural decline associated with aging when the compensatory mechanism is no longer sufficient. Further research to characterise other elements of the dopaminergic system (e.g. transporter density, receptor function) are needed to further understand the implications of these novel findings.

A possible connection between dopaminergic function and a predisposition to both psychopathology and drug use was also discussed. Once again the problem of establishing pre-existing differences comes into play here. However, as the poly-drug group were well matched on the use of all other recreational drugs, there seems little reason to expect a pre-disposition to ecstasy use in particular, rather than to stimulant use in general. Morgan et al. (2002a) showing that social environment changed levels of D_2 receptor availability in primates (see section 2.5). Could the intense sociability experienced by ecstasy users have also altered dopamine receptors in some way? This explanation is, of course, highly speculative.

As this is only the second study to investigate dopaminergic function in ecstasy users using neuroimaging techniques, and the first to investigate dopaminergic uptake, the results must be seen as preliminary. At the same time, they are intriguing, especially in the light of pre-clinical data that has found no evidence of long-term changes in dopaminergic function following MDMA administration which suggested a more complex relationship than simple MDMA-induced dopaminergic neurotoxicity. There is pre-clinical data implicating 5-HT in the modulation of dopamine (e.g. Bortolozzi et al., 2005; Pehek et al., 2006), and investigating this type of 'knock-on' effect may provide more insight into the

question of changes in dopaminergic function following ecstasy use. Clearly, further research is needed to elucidate these complex neurotransmitter interactions.

In the study described in Chapter 3 serotonin transporter density in ex-ecstasy users, poly-drug controls and drug-naïve controls was assessed with PET using the ^{11C}DASB ligand. A trend was observed towards poly-drug users having lower transporter binding than the drug-naïve controls. However, this difference no longer approached significance when the 3 participants who had used cocaine in the week prior to testing were removed from the analysis. These results replicate studies that make up a growing body of literature indicating no long-term reduction of SERT density in abstinent ecstasy users.

Thomasius et al. (2006) used a longitudinal design to assess SERT density with PET using the [^{11C}]McN5652 ligand, as well as cognitive function and psychopathology in ex- and current ecstasy users, poly drug controls and drug naïve controls at 2 follow up sessions at approximately 1 year intervals following an original test session. At all 3 test sessions the ex-users were not significantly different to controls in terms of SERT binding, and as such provide no evidence for either long-term or even permanent alterations in serotonergic axonal markers evident in primates years after cessation of ecstasy use. Interestingly, current users showed an increase in SERT binding across the test sessions following a reduction in ecstasy intake. This suggests that simply decreasing the amount of ecstasy ingested can prompt recovery. These findings could be interpreted as indicating a resilience in humans to MDMA-induced serotonergic injury compared to primates. On the other hand, it may simply highlight the fact that the methodologies used in animal studies investigating the neuropharmaocologicl effects of MDMA are not comparable to human recreational use and thus caution must be exercised when drawing conclusions about long-term effects in human users based on pre-clinical research.

This study also highlighted the importance of matching for poly-drug use, and in particular recent cocaine use. It is possible that reductions observed in current users in previous studies are partly due to recent cocaine use. This is particularly relevant considering data from the most recent British Crime Survey that indicates and

increase in cocaine use, and the data presented in Figure 8.1 suggesting that increasing numbers of ecstasy users are also using cocaine.

8.2 What are the mid-week effects of ecstasy use?

Chapter 6 adds weight to what is probably one of the most robust findings in the ecstasy research: lowering of mood several days after ecstasy use. This study replicated previous findings of increased self-rated aggression (Verheyden et al., 2002; Curran et al., 2004; Hoshi et al., 2004) and depression (Curran & Travill, 1997; Verheyden et al., 2002; Curran et al., 2004) as well as replicating Curran et al's (2004) results showing increased cognitive bias toward aggressive material in ecstasy users 4 days after taking the drug. A recent study by Huxter et al. (2006) found that although low mood in the days following ecstasy use was in part related to the co-use of alcohol, previous drug use and ecstasy's effects on sleep patterns, the change in mood remained significant even after controlling for all of these factors.

Evidence of gender differences in aggression, and in the effects of ecstasy (see section 1.10) lead to the hypothesis that there may be gender differences in mid-week aggression in ecstasy users. However, no evidence of this was found. As discussed fully in section 6.5.2, the lack of observed differences may be related to the *type* of aggression assessed. Overall, research appears to indicate that women show less direct aggression than men, whereas the task used in this study tapped a bias towards processing and recognising information with aggressive content. Gender differences in the long-term effects of ecstasy use have not been addressed in this thesis as all participants in chapters 2, 3, 4 & 5 were male. This was due to ethical restrictions in relation to PET scanning and radiation exposure in women of child bearing age. In future it would be preferable to assess both women and men in order to further explore the possibility of gender differences in the effects of ecstasy use both in the short and long-term.

8.2.1 Are the transient mood changes caused by temporary 5-HT depletion?

The main explanation given for the 'mid-week blues' is that 5-HT is depleted for several days following consumption of MDMA due to the attenuation of tryptophan hydroxylase. It could, however, be argued that as some previous studies have found

increased depression and aggression in abstinent ecstasy users (e.g. MacInnes et al., 2001; Gerra et al., 2002), it is possible that when tested several days after ecstasy use the participants have simply returned to their usual mood levels after the high of the weekend. On the other hand, several lines of research support the idea of transient lowering of mood in the days following ecstasy use. Studies into the sub-acute effects of ecstasy use have found no significant differences in trait aggression/depression between ecstasy users and controls. In addition, Curran et al. (2004) found that self-rated mood was not significantly different in the same participants 7 days after ecstasy use whereas 4 days after they rated themselves as significantly more aggressive and depressed than controls. Problems associated with self-rated measures have been discussed previously, and using the more objective interpretative bias task to provide evidence of mid-week aggression in ecstasy users went some way to overcoming these issues. Finally, the results reported in Chapter 5 support the notion that increased bias toward aggressive material is a transient phenomenon in ecstasy users as no evidence was found for increased aggression using the same task in ecstasy users abstinent for an average of approximately 2 weeks.

Tryptophan depletion could theoretically model the reduction of 5-HT following ecstasy use. However, the results from previous research with healthy volunteers in mixed: tryptophan depletion does not always affect mood (see Young & Leyton, 2002), for review). Bond (2005) points out that increases in aggression following tryptophan depletion in previous research appear to be dependent on several conditions, one of which is participants' levels of trait aggression or hostility. This suggests a *vulnerability* to increased aggression following reduction of 5-HT synthesis. It is possible that the effect seen in ecstasy users is an 'acute on chronic' effect in that regular ecstasy users have not fully regained levels of serotonin between ecstasy-using sessions and thus the depleting effect of the drug is more severe than tryptophan depletion in non-drug using volunteers. Although only 2 previous studies have investigated aggression following tryptophan depletion in women (Bond et al., 2001; Marsh et al., 2002) both found increases. These studies support the findings of this thesis of no gender differences in mid-week aggression as previous research gives no reason to expect gender differences following 5-HT depletion caused by ecstasy use.

Although evidence strongly suggests that mid-week lowering of mood occurs in ecstasy users, the lack of direct measure of 5-HT means that it is difficult to provide objective evidence that these effects are caused by transient serotonin depletion. In Chapter 7, I attempted to address this issue by using an indirect assessment based on previous studies by Harmer and colleagues of the effects of pharmacological manipulations of 5-HT. This research has shown that increasing serotonin via administration of either tryptophan or citalopram *improved* recognition of fear, and that reducing serotonin via tryptophan depletion *impairs* fear recognition. I therefore argued that these manipulations could model the effects of ecstasy acutely and in the days following administration and that therefore the same effects could be expected when assessing recognition of fearful facial expressions in ecstasy users on the night of drug use and several days after. Although the effect was subtle, by showing improved fear recognition on day 0 and impaired fear recognition on day 4 the results of the study supported the original hypothesis. In a recent study, Yip & Lee (2005a) found no difference in fear recognition between abstinent ecstasy users and controls, again supporting the notion that the effects on fear recognition observed are transitory. Interestingly, that study found ecstasy users were impaired on recognition of both disgust and sadness. Further research is needed to investigate facial expression recognition in ecstasy users.

In future it would be interesting to use a similar method and assess ecstasy users on other tasks that have previously been shown to be affected by serotonergic manipulations (e.g. an affective Go/No go task, Murphy et al., 2002). In addition, the use of more objective measure of depressed mood, such as the Autobiographical Memory Test (Williams & Broadbent, 1986) that is sensitive in depressed patients, would be useful in order provide evidence for mid-week depressed mood that is not based solely on self-ratings. Of course, the strongest evidence to support the idea of transient serotonergic depletion in the days following ecstasy use would be a direct measure of serotonergic function applied at several distinct time points, after acute administration of MDMA in both naïve and regular ecstasy users. However, no direct measure of brain 5-HT exists. More indirect measures, such as CSF or plasma 5-HIAA, are both difficult to carry out and can be affected by factors such as season, age and diet (Blennow et al., 1993; Brewerton et al., 1988; Grimes et al., 2000).

8.3 Future directions

"The first step towards knowledge is to know that we are ignorant"

Richard Cecil

I believe that in order to move forward in understanding the long-term effects of ecstasy use it is essential to move on the assumptions often made about the effects of MDMA in humans based on pre-clinical evidence. Although animals show 5-HT neurotoxicity following MDMA administration, very few behavioural changes have been identified, whereas a wide range of behavioural changes are found in human ecstasy users and these are attributed to 5-HT neurotoxicity caused by MDMA administration. There seems to be a gap in the logic behind this explanation. The equivocal nature of the findings from within the field point to a more complex relationship than one based on simple cause and effect.

Although many authors have used the findings of correlations between levels of ecstasy use and cognitive performance as evidence for this direct relationship, as discussed previously, amount of ecstasy used is a dubious measure. Not only is self-report for drug use notoriously unreliable, but the amount and purity of MDMA in ecstasy tablets varies. This idea is supported by the fact that the observed deficits across many studies vary irrespective of how much ecstasy the participants report using. For example, Yip & Lee (2005b) found a range of cognitive impairments in ecstasy users who had taken the drug an average of approximately 36 occasions in their lifetimes, whereas participants who had used it approximately 275 times have been found to have no impairments (Roiser et al., 2005b). Participants in Chapter 4 had used it a similar number of times as those sampled by Roiser et al. (2005b) and again little evidence of cognitive impairments were found. There is a paradox in that although the pre-clinical data has consistently found evidence of reductions in serotonergic function it has failed to identify long-term behavioural changes, whereas a wide range of behavioural changes have been related to ecstasy use in humans. It is, of course, possible that the greater complexity of the human brain and of its functions (e.g. linguistics) means it is more susceptible to neurochemically-induced behavioural changes.

One possible way to move forward in research is to attempt to unravel the concept of differing levels of pre-existing susceptibility in sub-groups of ecstasy users. Susceptibility may relate both to the serotonergic changes following ecstasy use and the behavioural effects of these changes. By looking at broader psychopharmacological research we can discern evidence suggesting that there are differences in serotonergic vulnerability. Healthy volunteers with a family history of depression are more likely to exhibit lowered mood following acute tryptophan depletion (see Riedel et al., 2002b, for review). Both people with high trait impulsivity and healthy volunteers with family history of psychiatric illness are more vulnerable to cognitive impairments following tryptophan depletion (Cools et al., 2005; Sobczak et al., 2002). Varying vulnerabilities to serotonergic challenges could be related to genetic differences, for example polymorphisms of the 5-HT transporter (5-HTT) gene. Neumeister et al. (2002) investigated the mood effects of tryptophan depletion in women with and without family histories of depression who were also genotyped for the 5-HTT polymorphism. They found that women with the *ss* genotype showed increased depression following tryptophan depletion irrespective of whether they had a positive family history for depression or not. Women with the *ll* genotype, showed the opposite pattern: they were *less* likely to experience depression following the procedure irrespective of family history. In *sl* participants, those with positive family history were more likely to have increase depression following tryptophan depletion. Although the numbers in the sub-groups of participants in this study were small (4-10 participants in each group), it provides some fascinating insight into the possible role of genetics in susceptibility to serotonergic changes. These types of findings are relevant to ecstasy research, and in future it is important to attempt to elucidate the role of genetics in the effects of MDMA.

At the summer meeting of the British Association of Psychopharmacologists in 2004, one symposium posed a question that has yet to be answered: "Ecstasy: benign pleasure or potential plague?". A possible link between ecstasy use and cognitive impairment and increased levels of psychopathology has been indicated by previous research. However, if a simple causal relationship existed between MDMA consumption and 5-HT neurotoxicity, and led to these effects, the sheer numbers of people using ecstasy could pose a substantial public health problem in

the UK. It is generally assumed that the majority of ecstasy users do not experience problems severe enough to prompt them to seek professional help - they lead normal lives and eventually stop taking the drug. Only 5/53 ecstasy users tested in Chapters 2-5 reported seeking help for a previous mental health problem. Although a recent book on drug abuse described the potential for addiction to ecstasy as 'moderate', placing it in the same category of addictive potential as alcohol and cocaine (West, 2006), there is no evidence of ecstasy users becoming dependent on the drug, or experiencing cravings for it. In addition, despite evidence of ecstasy users developing a tolerance to the drug (Parrott, 2005), all of the ex-users tested in this thesis reported having experienced no problems quitting ecstasy use, and did not relapse after cessation. This is supported by Verheyden et al. (2003b) who found that approximately 90% of ex-users interviewed did not relapse after quitting ecstasy use.

However, it is possible that the low number of mental health problems reported in the ecstasy users in this thesis arose from a selection bias. Verheyden et al. (2003b) interviewed 66 ex-ecstasy users and found that their reasons for quitting were either based on mental health problems or circumstantial reasons. A striking difference between these 2 groups was that 62.2% of those giving mental health reasons had sought professional help for mental health problems compared to only 27.6% of those who had stopped for circumstantial reasons. In addition, the 30 participants who took part in the ^{11C}DASB PET scan were screened to ensure that they did not have either a personal or family history of depression as this could have confounded the results from the scanning data. Is it possible that ecstasy use is causing an increase in depression that has not as yet been identified? The number of prescriptions for antidepressants rose in England alone from 9 million in 1992 to 29 million in 2004 (Figure 8.2). Although this is likely to partly reflect reduced prescribing of benzodiazepines and increased GP awareness of depression, it is possible that it also reflects increased depression following ecstasy use, albeit undisclosed to GPs. The most recent British Crime Survey (2004/05) estimated that approximately 2 million people aged 16-59 yrs had taken ecstasy, a number that could account for some proportion of the increase in antidepressant use. On the other hand, it may simply reflect the coincidental rise of ecstasy at the same time as the rise of the 'Prozac nation'. In fact, in the early nineties when ecstasy was being

portrayed in the media as a deadly drug, Prozac was being touted as the new wonder drug.

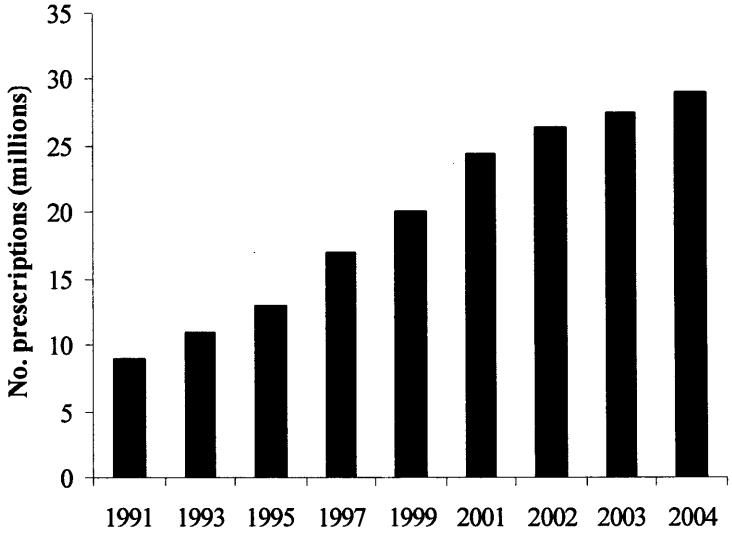


Figure 8.2: Number of antidepressant prescriptions in England 1991-2004

Source: Department of Health statistical bulletins - prescriptions dispensed in the community

A 'time bomb' theory of MDMA neurotoxicity has also been suggested, whereby the problems caused by MDMA may not manifest themselves for several years. Serotonin transporter density has been found to decline by approximately 10% per decade in healthy humans (Yamamoto et al., 2002), and healthy participants with an average age of 59yrs had reduced ^{18}F-dopa uptake compared to a group with an average age of 27yrs (Kumakura et al., 2005). It is possible that in the long-term, ecstasy users will be more severely affected by these normal age-related declines.

One-off cross-sectional studies are no longer sufficient to extend our knowledge relating to the complex question of the long-term effects of ecstasy. In future it is essential to combine methodologies such as neuroimaging techniques, genetics and neurocognitive assessments to provide a more comprehensive picture. Ideally, prospective, longitudinal studies could be carried out over years so that individual differences could be accounted for and better understood. However, even this type of design presents problems. In the western world ecstasy is becoming established as just one of the many substances used in the cocktail of psychoactive drugs used by recreational users. A prospective study recruiting from Holland's cannabis-

friendly coffee shops was initiated in 2002 (Reneman, personal communication), but failed to find many new recruits to ecstasy over the following years. This study may be inconclusive simply because the small sample size reduces its statistical power. It may be more useful to recruit in countries where ecstasy use is a new phenomenon. For example, Yip & Lee (2005a; 2005b) recruited an unusual sample of 100 ecstasy users who had not used other recreational drugs in Hong Kong. Although there are many other countries where ecstasy has only very recently started to be used by young people, such as Iran, recruiting and investigating in such countries presents a myriad of ethical and political considerations.

8.4 Therapeutic use of MDMA

Possibly one of the most intriguing aspects of the acute effects of MDMA is its empathic effects, unique among stimulants and hallucinogens. This uniqueness could indicate a potential for MDMA to become a pharmacological tool in understanding this extraordinary human trait. In recent years, the processes that underpin empathy have become "a subject of intense interest within the social neurosciences" (Singer et al., 2006). Neuroimaging studies investigating the neural basis of empathy have found that activation is seen in the same neuronal systems when people experience things such as disgust (Wicker et al., 2003) or pain (Jackson et al., 2005) themselves as when they see another experience it. Intuitively one would expect a more complex process to be involved in empathy than simply observing the experiences of others and experiencing them in the same way as we do ourselves. This was examined in a recent neuroimaging study by Singer and colleagues (2006). Participants first played a game with a confederate who either used fair or unfair strategies. Following the game participants rated those that had played fairly as more agreeable and likable than those that had played unfairly. Participants were then scanned while both they and the confederates received painful stimuli via electrodes to the hand. The results showed that, in male participants, the level of 'empathic' activation was less for the unfair players compared to the fair players. These fascinating results demonstrate the role of our emotional appraisal of an individual in our empathic response to them. Lack of empathy is seen in clinical populations, such as Antisocial Personality Disorder, which seem relatively irresponsive to current psychiatric medication. It is possible that MDMA's empathic 'ingredient' could be isolated to develop a drug treatment

which increases feelings of closeness and openness to others and therefore increase the neuronal response that could underpin empathy.

It is these feelings of openness and closeness to others that first inspired the use of MDMA as an adjunct to psychotherapy in the 1970's. However, the negative media publicity surrounding the drug hampered efforts to start clinical trials into its efficacy as a 'medicine'. Newspaper headlines such as "A night of ecstasy, a taste of death" (*Evening Standard*, 14.01.92) and "Ecstasy will rot your brain" (*Daily Record*, 14.06.96), along with highly publicised ecstasy related deaths such as that of Leah Betts in 1995, set the tone of the media's, and therefore the majority of the public's, view of ecstasy. This type of publicity, along with both the British and American governments' hard line 'war on drugs' policies, made research the possible therapeutic properties of MDMA extremely difficult.

Charles Grob (2000) observed that "for years fears aroused by the publicization of neurotoxicity concerns have stalled development of alternative research paradigms". Recently, however, a number of studies have gained approval to investigate the use of MDMA in the treatment of Post Traumatic Stress Disorder (PTSD), pain and for anxiety in advanced-stage oncology patients. The Multi-disciplinary Association of Psychedelic Studies (MAPS) are putting together a $5 million plan to extended these areas of research and develop MDMA as a prescription medicine. In his thoughtful introduction to a special edition of *Psychopharmacology* focusing on MDMA, Richard Green (2004) quotes Paracelcus (1293-1541): "The right dose differentiates a poison from a remedy". It remains to be seen whether this will be the case with MDMA, and although opinion is still divided in the scientific community of ecstasy research, the results of these trials are eagerly awaited.

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Appendices

Appendix 1: Ethics approval letters and volunteer information sheets for the studies presented in Chapters 1 & 2

Hammersmith and Queen Charlotte's & Chelsea Hospitals
Research Ethics Committee

BSc MA - Secretary

2nd Floor, Commonwealth Building
Hammersmith Hospital
Du Cane Road
London
W12 0NN

e-mail:
www.geocities.com/hammersmith_lrec

Dr.
PET Neuroscience
MRC/Cyclotron Unit

23/10/2003

Dear

2003/6645 Dr.	- Prof	- Prof	- Dr	- Dr Z	-
PET Neuroscience					

Long-term effects of MDMA ('ecstasy') on dopaminergic and serotonergic neurons: a PET study -

The Research Ethics Committee has **APPROVED**, from the ethical standpoint, the above research project involving investigations on human subjects for a period of four years from **23/10/2003** until **22/10/2007**. In any further correspondence about this project would you please quote the Project Registration Number: **2003/6645**.

N.B. Approval by a Research Ethics Committee does not automatically mean that the study may proceed. It is the responsibility of the NHS body under whose auspices the research is to take place to decide whether or not a study should go ahead, taking account of the ethical advice of the Committee. Investigators should seek approval from the relevant NHS body before proceeding with the study. Contact the HHT R&D office on for further information.

The committee's membership list, standing orders and GCP compliance statement may be downloaded from: **www.geocities.com/hammersmith_lrec**
if required for your records.

Would you please note that:

- **If the study is to take place at another site within this Health Authority then the local researcher is required to complete the 'Health Authority Locality Form' (which can be downloaded from www.corec.org.uk) and submit it to the appropriate LRECs along with the information sheet(s), the 'lead LREC' application form and the 'lead LREC' correspondence including this approval letter in the quantities required by the respective LRECs.**

(NB Studies taking place at Hammersmith and or Charing X Hospital sites only require ethical approval from either Hammersmith or Riverside LRECs – ethical approval from either committee covers all Hammersmith Hospital NHS Trust sites)

- ***(if applicable)*** the form of consent must be read and signed by each subject, or, if, with the specific agreement of the Committee, oral consent is permitted, that the oral consent of each subject must be appropriately recorded, and that the consent forms or records must be kept for subsequent examination, if required, by the Committee. **In addition copies of ALL signed patient consent forms should be sent to the Hammersmith Hospitals Trust's central repository for safe-keeping. Signed consent forms should be sent to:**

Appendix 1 continued

Consent Form Repository
HHT R&D Office
Hammersmith House
Hammersmith Hospital

- the committee requires reports to be sent to the REC Secretary annually and upon completion of the study using the report forms included in the application form.
- information concerning this study submitted to the committee may be given to the Hammersmith Hospitals Trust R&D Office. If you do not wish this information to be shared please inform the Secretary.
- **(if applicable)** the protocol number must be recorded on the notes of each subject;
- proposed changes to investigative protocols as approved, must be referred to the Secretary of the Research Ethics Committee, including changes made to the list of investigators;
- the study may be subject to future audit to ensure that it has been conducted in accordance with the application submitted to and approved by the REC and the host institution.
- any untoward occurrence in connection with procedures carried out under this protocol, whether due to negligence or otherwise, must be reported to the Secretary of the Research Ethics Committee without delay.
- that if clarification is needed on any matter at issue, reference must be made back to the Secretary of the Research Ethics Committee.

The Committee undertakes to adhere, as far as is consistent with its Constitution, to the ICH Harmonised Tripartite Guideline for Good Clinical Practice (ICH/GCP).

The following items have been reviewed in connection with the above study:

Original LREC application form dated: 28/07/2003
Participant Information Sheet(s): signed 23-10-03 by REC Chairman
Principal Investigator's C.V.
UCL non-NHS ethics committee approval letter dated 29-9-03; revised application v2

Appendix 1 continued

The Graduate School
University College London
Gower Street London WC1E 6BT

Professor
Head of the Graduate School

29 September 2003

Professor
Professor of Psychopharmacology
Psychopharmacology Laboratories
Sub-department of Clinical Health Psychology
UCL
Torrington Place
London
WC1E 6BT

Dear Professor

Re: Notification of Ethical Approval

Project ID: 0051/002: Long-term effects of recreational drug use on information processing and mood

The above research has been given ethical approval following review by the UCL Committee for the Ethics of non-NHS Human Research for a period of 12 months from the commencement of the project (1 October 2003) subject to the following conditions:

1. It is a requirement of the Committee that research projects which have received ethical approval are monitored annually. Therefore, you must complete and return our 'Annual Continuing Review Approval Form' PRIOR to the 1 October 2004. If your project has ceased or was never initiated, it is still important that you complete the form so that we can ensure that our records are updated accordingly.

2. You must seek Chair's approval for proposed amendments to the research for which this approval has been given. Ethical approval is specific to this project and must not be treated as applicable to research of a similar nature. Each research project is reviewed separately and if there are significant changes to the research protocol you should seek confirmation of continued ethical approval by completing the 'Amendment Approval Request Form'.

The forms identified above can be accessed by logging on to the ethics website homepage: http://zzz.grad.ucl.ac.uk/ethics/ and clicking on the button marked 'Key Responsibilities of the Researcher Following Approval'.

3. It is your responsibility to report to the Committee any unanticipated problems or adverse events involving risks to participants or others. Both non-serious and serious adverse events must be reported.

Appendix 1 continued

Letter to Professor Curran 29/09/2003

Reporting Non-Serious Adverse Events.
For non-serious adverse events you will need to inform Ms Ethics Committee Administrator within ten days of an adverse incident occurring and provide a full written report that should include any amendments to the participant information sheet and study protocol. The Chair or Vice-Chair of the Ethics Committee will confirm that the incident is non-serious and report to the Committee at the next meeting. The final view of the Committee will be communicated to you.

Reporting Serious Adverse Events
The Ethics Committee should be notified of all serious adverse events via the Ethics Committee Administrator immediately the incident occurs. Where the adverse incident is unexpected and serious, the Chair or Vice-Chair will decide whether the study should be terminated pending the opinion of an independent expert. The adverse event will be considered at the next Committee meeting and a decision will be made on the need to change the information leaflet and/or study protocol.

4. On completion of the research you must submit a brief report (a maximum of two sides of A4) of your findings/concluding comments to the Committee which includes in particular issues relating to the ethical implications of the research.

Yours sincerely,

Chair of the UCL Committee for the Ethics of Non-NHS Human Research

Appendix 1 continued

Information Sheet for Research Participants

You will be given a copy of this Information Sheet

Study title

Long-term effects of 'ecstasy' on human brain: a PET study

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

We will be happy to let you have a copy of the leaflet entitled 'Medical Research and You' published by Consumers for Ethics in Research (CERES). This leaflet gives more information about medical research and looks at some questions you may want to ask. Thank you for reading this.

What is the purpose of the study?
Use of recreational drugs such as MDMA ("ecstasy") is becoming increasingly common among people in their late teens to early thirties. Some studies suggest that long-term use of drugs like 'ecstasy' can affect people's concentration, mood and possibly slow their movements. Animal studies show that 'ecstasy' may cause such effects by altering the levels of two types of chemical in brain, called dopamine and serotonin.

At the Cyclotron Building at Hammersmith Hospital in London, we perform a special type of brain scans, called positron emission tomography (PET) scans, to measure chemical changes in the brain and to study how the brain works. The purpose of this study is to find out how 'ecstasy' affects the dopamine and serotonin levels in human brains by using different types of PET scan, and to see if such effects persist in people who have stopped using 'ecstasy'.

Why have I been chosen?
You have been asked to take part in this study because you fulfil the criteria of one of the categories below:

1. People who have used 'ecstasy' on a regular basis (more than 20 occasions) in the past but have not used 'ecstasy' for at least 1 year
2. People who have never used 'ecstasy' but who regularly use a range of other recreational drugs
3. People who have never used recreational drugs

As users of 'ecstasy' often use other drugs concurrently, these drugs may interfere with our ability to interpret the results from the PET scans. Therefore, we need to include 3 groups of participants to minimise such interference.

Do I have to take part?
It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. You are free to withdraw at any time and without giving a reason. A decision to withdraw or not to take part will not affect the standard of care you receive.

What will happen to me if I take part?
You will have agreed to participate in the first part of the study organised by Professor Curran at University College London. If you agree to take part in the PET study you will be expected to refrain from:

- drinking more than 3 units of alcohol for 24 hours prior to the session.
- taking any illicit drug for at least 3 days prior to the study session.

We aim to perform 2 types of PET scans, one to look for changes in dopamine system, and another to look for changes in serotonin system. You will be randomly allocated to have 1 of these 2 types of PET scans whenever possible. However, we will also take into account your personal preference and availability of scanning slots for a particular type of scan.

Just before the scan, we will insert a small needle into a vein in your arm. This is a simple procedure like a blood test. We then will inject a radioactive compound called a tracer. Each PET scan lasts 1.5-2 hours. During the scan, you will be asked to lie still on your back on a couch with your head resting in the scanner.

If you are having a serotonin scan, we will need to insert an additional small needle into an artery over your wrist. A local anaesthetic will be given to minimise any discomfort. Blood samples will be taken from this needle to measure the level of radioactivity in your blood. Some of the blood samples will be used to look for any differences in the genetics of the serotonin system including the receptors as this may affect the PET scan results. This data will be coded and will only be accessible to investigators involved with the study. The total amount of blood we will take is about 200 mls. To put this in context, when you donate blood you give about 450 mls each time.

If you are having a dopamine scan, you will also be asked to take some tablets called carbidopa and entacapone one hour before the scan. These are designed to boost the scan signals and should not cause any side effects.

In addition, you will also be asked to have a magnetic resonance scan (MRI). This is a detailed structural picture of the brain and does not involve any additional radiation. This scan takes about 15-20 minutes, and will usually be performed on

the same day as the PET scan. Therefore, you need to make only one trip to the Hammersmith Hospital.

You will also be asked to give a urine specimen and about 50 strands of hair (to be removed by scissors) so that we can perform an accurate estimation of your 'ecstasy' use/abstinence in the past. The specimens will be coded and you will not be identified on them.

No other lifestyle restrictions will be placed on you if you participate in this study.

Why are we taking samples for genetic tests and what will happen to them?
The main reason for taking blood samples is to understand the influence of differences in genetic structure on brain function in psychiatric illnesses. Various research groups around the world have described differences in genetic structure and related them to changes in brain function. We would like to see if these differences might account for some of the changes caused by ecstasy on brain serotonin transporters, if any.

You need to be aware that once you have given the blood sample you will not have any retained rights to the sample. The sample will be coded and stored in a freezer in the Department of Psychiatry. These investigations are unlikely to have any implications for you personally so we do not provide results of the genetic tests to individual participants. We will store these samples in a freezer so that if new genes are implicated in the measures of brain function we are interested in, we can analyse your original samples without having to ask you back.

What are the possible disadvantages and risks of taking part?
The insertion of needles into your vein and artery may cause some temporary, mild discomfort and local bruising. If you are claustrophobic, you may find MRI slightly difficult to tolerate.

The total radiation dose you will receive from the PET scans is slightly less than the background radiation to which you are exposed to in a year, simply by living in the UK. You should also inform us if you have participated in any study involving radiation over the last 12 months.

If you experience any problems following the PET scan such as bleeding from the arterial puncture site, you should seek medical help from your GP or local hospital in the first instance.

You should be aware that there is a possibility that the methods used in this study may produce an unexpected result that may have relevance for your health. In the unlikely event of this happening, we will discuss this with you and, if necessary,

provide any support that you may require, such as arranging follow-up tests and/or treatment.

What are the possible benefits of taking part?
This study will enhance our understanding of long-term effects of 'ecstasy' on human brains. You will also be paid £50.00 plus travel expenses for participating in the PET study.

What if something goes wrong?
If you are harmed by taking part in this research project, you will be eligible to apply for compensation through the Imperial College School of Medicine's "No Fault" Compensation Scheme.

Will my taking part in this study be kept confidential?
All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised from it.

What will happen to the results of the research study?
The results from this study may be published in a medical journal. However, you will not be identified in any publications. The results of the PET study will not be available to you individually. The PET scans may identify abnormalities in some participants, and the long-term significance of these findings may yet be unclear. Therefore, we shall not reveal the results to you at this stage. If the impact of such findings on your health can be ascertained in the future, we may, with your agreement, discuss them with you.

Who is organising and funding the research?
Medical Research Council of the United Kingdom is funding the research. The investigators will not receive any financial rewards for recruiting patients for this trial.

Who has reviewed the study?
The Hammersmith, Queen Charlotte's & Chelsea and Acton Hospitals Research Ethics Committee.

Contact for Further Information
If you have any questions or concerns, please do not hesitate to telephone Dr
Dr or Dr

If you agree to have the scans, you will be asked to sign a consent form. You will be given a copy of the information sheet to keep for your records.

Thank you for your interest in the study.

Appendix 1 continued

Sub-Department of Clinical Health Psychology
UNIVERSITY COLLEGE LONDON
GOWER STREET LONDON WC1E 6BT

Professor
UCL : 020 7679 1898
Code from overseas: +44 20
Fax: 020 7916 1989

VOLUNTEER INFORMATION LEAFLET 1

Long-term effects of recreational drug use on information processing and mood

Use of recreational drugs such as cannabis, MDMA ("ecstasy") and/or cocaine is widespread in many countries and some argue it is now the norm rather than the exception among people in their late teens to early thirties. The latest data indicate that there are nearly half a million MDMA ('ecstasy') users in the United Kingdom. Some studies suggest that long-term use of drugs like MDMA can affect people's concentration and mood. However, nearly all MDMA users also use a range of other recreational drugs so it is difficult to know which drug or drug combination causes these effects.

The purpose of this study is to investigate whether these memory/mood effects are related to use of other recreational drugs and whether they persist in those people who stop using MDMA .

There is a second stage to this study which investigates whether there are also changes in levels of two chemicals in the brain that are affected by MDMA: dopamine and serotonin. This second part of the study involves you having brain scans. It is being conducted by doctors at Hammersmith Hospital's Cyclotron Building. You have been given a separate information sheet about the second part of the study (Information Sheet 2) and you will be able to discuss taking part with the doctors at the Hammersmith. The rest of this information sheet concerns part 1 of the study. If you agree to take part, you will be asked to sign a consent form for the first part of the study only.

Do I have to take part?
Your participation in the study is entirely voluntary and you are free to withdraw from the study at any time, even if you have previously given your written consent. If you do agree to take part, you will be asked to sign a consent form and will be given this information sheet to keep. Agreeing to take part in the first part of the study does not oblige you to take part in the second part.

What will happen to me if I take part?
You will first be interviewed on the telephone to see if you meet the study entry criteria. A second appointment will be made for you to do the study itself. This involves completing a

series of straightforward pencil and paper tests, questionnaires and some computer based tasks. The session will last for approximately 2 hours and you will have a rest break in the middle. You will also be given an appointment to see the doctors at the Hammersmith Hospital for the second stage of the study. This involves a scan of your brain (a PET scan) as detailed in the information leaflet. You will be invited to discuss your participation with Dr Paola Piccini and her colleagues. If you agree to take part, you will be asked to sign a consent form for the second part of the study

What do I have to do?
If you agree to take part in the study you will be expected to:

- Refrain from drinking more than 3 units of alcohol for 24 hours prior the session.
- Refrain from taking any illicit drug for at least 3 days prior to the study session.

What are the possible benefits of taking part?
By taking part in this research study you will contribute to helping us to establish the long-term effects of recreational drugs. The results of the study will enable us to make recommendations and advise people who plan to or actually take ecstasy. You will receive a payment of £7.50 per hour of your time, and your travel expenses will be reimbursed.

Will my taking part in the study be kept confidential?
Data will be collected and stored in accordance with the Data Protection Act 1998. Any information you give about yourself, your medical history and the results of any tests will be will be held in complete confidence and will not be made public or disclosed to anyone other than the investigators. If the results of the study are published for scientific purposes, you will not be identified. You will receive feedback when the study is completed.

Who should I contact for further information?
Any questions you may have about the study should be directed to Rosa Hoshi who is contactable by telephone on (office) or by email: ; or to [illegible] you may also contact Prof.

Approved by University College London's Committee on the Ethics of Non-NHS Human Research.

Appendix 2: Mean (SD) scores of ex-ecstasy users, poly-drug controls and drug-naïve controls in cognitive tests which showed no significant group differences (Chapter 2)

	Ex-ecstasy users	Poly-drug controls	Drug-naïve controls
Immediate prose recall	7.14 (3.49)	5.39 (2.11)	7.29 (2.44)
Delayed prose recall	5.96 (3.42)	4.07 (2.42)	5.96 (2.92)
Serial sevens total score	23.71 (10.25)	19.29 (9.30)	23.58 (12.54)
Serial sevens errors	0.93 (1.49)	1.50 (1.74)	1.42 (1.38)
Phonemic verbal fluency	18.93 (3.97)	17.50 (3.32)	18.08 (3.90)
Phonemic verbal fluency errors	0.29 (0.61)	0.86 (0.86)	0.33 (0.49)
Category fluency	23.00 (5.43)	19.93 (4.81)	23.08 (6.11)
Category fluency errors	0.64 (0.84)	0.71 (1.14)	0.58 (0.67)
TMT time A (ms)	28.22 (7.97)	28.03 (7.43)	22.42 (5.03)
TMT errors A	0.36 (0.63)	0.42 (0.36)	0.67 (0.39)
TMT time B (ms)	61.26 (23.59)	61.59 (20.18)	56.65 (22.82)
TMT errors B	0.36 (0.93)	0.43 (0.85)	0.23 (0.29)
Gibson's time (ms)	46.19 (9.16)	44.15 (13.27)	46.98 (11.26)
Gibson's errors	2.07 (2.23)	3.14 (2.25)	1.67 (2.46)
SWM between errors	13.69 (14.61)	17.00 (13.00)	9.36 (15.75)
SWM strategy	28.92 (5.95)	30.64 (4.60)	30.09 (6.41)
RVIP total hits	32.54 (9.07)	30.29 (12.09)	35.64 (8.78)
RVIP total false alarms	8.38 (3.55)	27.00 (51.33)	12.82 (51.33)
RVIP mean reaction time for hits (ms)	462.73 (68.19)	477.05 (103.19)	473.75 (106.27)

Appendix 3: Mean (SD) scores of ex-ecstasy users, poly-drug controls and drug-naïve controls in cognitive tests which showed no significant group differences (Chapter 3)

	Ex-ecstasy users		Poly-drug controls		Drug-naïve controls	
Immediate prose recall	7.14	(3.08)	5.94	(1.78)	7.50	(3.58)
Delayed prose recall	5.68	(3.20)	4.67	(1.62)	6.25	(4.12)
BSRT trial 1	6.45	(1.21)	6.00	(2.06)	6.50	(1.27)
BSRT trial 2	9.27	(2.28)	7.89	(2.37)	8.90	(2.47)
BSRT trial 3	10.36	(1.91)	9.56	(3.00)	11.30	(2.36)
BSRT delayed trial	6.55	(2.02)	7.11	(3.44)	7.00	(3.74)
Serial sevens total score	23.18	(11.86)	21.89	(6.74)	26.70	(20.23)
Serial sevens errors	1.00	(1.84)	1.22	(1.30)	23.97	(13.86)
Phonemic verbal fluency	17.27	(4.69)	20.33	(5.43)	19.80	(4.64)
Phonemic verbal fluency errors	0.36	(0.50)	0.44	(0.73)	0.01	(0.95)
Category fluency	24.45	(4.37)	24.44	(4.72)	24.50	(5.74)
Category fluency errors	0.82	(1.08)	0.89	(1.27)	0.20	(0.42)
TMT time A (ms)	26.57	(9.01)	29.17	(8.53)	24.44	(6.28)
TMT errors A	0.27	(0.65)	0.11	(0.33)	0.00	(0.00)
TMT time B (ms)	67.49	(30.10)	60.94	(22.84)	64.56	(30.05)
TMT errors B	0.45	(1.03)	0.44	(1.01)	0.20	(0.63)
Gibson's time (ms)	47.86	(22.55)	45.52	(7.93)	44.63	(13.23)
Gibson's errors	3.00	(3.16)	2.11	(2.20)	2.50	(2.27)
SWM between errors	12.18	(12.05)	21.33	(26.00)	16.80	(20.33)
SWM strategy	27.55	(4.87)	31.00	(7.91)	31.20	(8.05)
SOC mean initial thinking time (ms)	13817.89	(9358.16)	9384.94	(4114.33)	10135.00	(5977.58)
SOC mean subsequent thinking time (ms)	733.83	(774.00)	931.95	(700.92)	1369.96	(1821.93)
SOC problems solved in minimum moves	9.91	(1.38)	9.11	(1.69)	9.80	(1.99)
RVIP total hits	32.45	(6.33)	32.50	(7.91)	30.80	(8.27)
RVIP total false alarms	6.11	(8.12)	12.38	(17.48)	8.30	(9.59)
RVIP mean reaction time for hits (ms)	550.05	(138.80)	538.84	(83.96)	1144.54	(1862.57)

Appendix 4: Ethics approval letter (amendment to previous approval) and volunteer information sheet for studies presented in Chapters 4 & 5

UCL Committee for the Ethics of Non-NHS Human Research

Amendment Approval Request Form

1. ID Number:	Name and Address of Principal Investigator:
0051/002	Prof

2. Title of Project:
Long-term effects of recreational drug use on information processing and mood

3. Information about the amendment:

(a) Is the amendment purely administrative? YES (NO) N/A

(b) Has the Participant Information Sheet/Consent Form been changed as a result of the amendment? YES If yes, please enclose a copy. Copy enclosed

4. Summarise the issues contained in the amendment. We wish to test an additional group of volunteers who are currently using MDMA. They will be assessed in exactly the same way as the 3 groups in the main study (ex-MDMA users; polydrug user; non-using controls). The other three groups have all been tested at UCL before they go to the Hammersmith for PET scanning and urine screens to check for recent drug use (local ethics approval has been given there). The additional group will not be involved in PET scanning and so we wish to do urine screens (for drugs of abuse) here at UCL. We have also amended the form to include the names of two 3rd year project students who will be assisting us in data collection. To test the additional group, we request an extension of the ethical approval of the project until October 2006.

5. Please give any other information you feel may be necessary:
The information sheet has been amended to include urine screen information.

Signature of Principal Investigator:

Date of Submission: 15-9-2005

FOR OFFICE USE ONLY:

Amendments to the proposed protocol have been ....approved..... by the Committee for the Ethics of Non-NHS Human Research.

Chair's Signature:

Date: 20.9.05

Appendix 4 continued

Sub-Department of Clinical Health Psychology
UNIVERSITY COLLEGE LONDON
GOWER STREET LONDON WC1E 6BT

Professor
UCL : 020 7679 1898
Code from overseas: +44 20
Fax: 020 7916 1989

VOLUNTEER INFORMATION LEAFLET version 2

Long-term effects of recreational drug use on information processing and mood

Use of recreational drugs such as cannabis, MDMA ("ecstasy") and/or cocaine is widespread in many countries and some argue it is now the norm rather than the exception among people in their late teens to early thirties. The latest data indicate that there are nearly half a million MDMA ('ecstasy') users in the United Kingdom. Some studies suggest that long-term use of drugs like MDMA can affect people's concentration and mood. However, nearly all MDMA users also use a range of other recreational drugs so it is difficult to know which drug or drug combination causes these effects.

The purpose of this study is to investigate whether these memory/mood effects are related to use of other recreational drugs and whether they persist in those people who stop using MDMA. People who have stopped using MDMA have already taken part in this research. We are now inviting people who are current users of MDMA to take part.

Do I have to take part?
Your participation in the study is entirely voluntary and you are free to withdraw from the study at any time, even if you have previously given your written consent. If you do agree to take part, you will be asked to sign a consent form and will be given this information sheet to keep.

What will happen to me if I take part?
You will first be interviewed on the telephone to see if you meet the study entry criteria. An appointment will be made for you to do the study itself. This involves completing a series of straightforward pencil and paper tests, questionnaires and some computer based tasks. The session will last for approximately 2 hours. Prior to the tests you will provide a urine sample to verify that you have not used recreational drugs for at least 4 days.

What do I have to do?
If you agree to take part in the study you will be expected to:

- Refrain from drinking more than 3 units of alcohol for 24 hours prior the session.
- Refrain from taking any illicit drug for at least 4 days prior to the study session. This will be verified using a urine screening.

Appendix 1 continued

What are the possible benefits of taking part?
By taking part in this research study you will contribute to helping us to establish the long-term effects of recreational drugs. The results of the study will enable us to make recommendations and advise people who plan to or actually take ecstasy. You will receive a payment of £20 for your time.

Will my taking part in the study be kept confidential?
Data will be collected and stored in accordance with the Data Protection Act 1998. Any information you give about yourself, your medical history and the results of any tests will be will be held in complete confidence and will not be made public or disclosed to anyone other than the investigators. If the results of the study are published for scientific purposes, you will not be identified. You will receive feedback when the study is completed.

Who should I contact for further information?
Any questions you may have about the study should be directed to –
You can also contact Rosa Hoshi -
email:

Approved by University College London's Committee on the Ethics of Non-NHS Human Research.

Appendix 5: Mean (SD) scores of ex-ecstasy users, poly-drug controls and drug-naïve controls in cognitive tests which showed no significant group differences (Chapter 4)

	Ex-ecstasy users	Current ecstasy users	Poly-drug controls	Drug-naïve controls
Immediate prose recall	7.18 (3.09)	7.50 (2.80)	5.71 (1.89)	7.11 (2.92)
Delayed prose recall	5.86 (3.14)	5.96 (2.79)	4.41 (1.99)	5.93 (3.41)
Serial sevens total score	23.50 (10.33)	24.76 (11.11)	21.59 (10.01)	25.07 (15.06)
Serial sevens errors	1.04 (1.55)	1.24 (1.20)	1.24 (1.43)	1.78 (1.40)
Phonemic verbal fluency	18.07 (4.13)	17.36 (5.92)	17.76 (3.68)	19.96 (5.31)
Verbal fluency errors	0.32 (0.55)	0.52 (0.92)	0.66 (0.77)	0.44 (0.70)
Category fluency	23.50 (5.17)	22.60 (6.48)	22.48 (6.17)	23.96 (6.20)
Category fluency errors	0.79 (9.17)	0.28 (0.54)	0.83 (1.14)	0.52 (0.89)
TMT time A (ms)	26.69 (8.33)	29.28 (11.46)	28.78 (7.74)	25.74 (9.03)
TMT errors A	0.29 (0.60)	0.28 (0.74)	0.17 (0.38)	0.11 (0.32)
TMT time B (ms)	63.60 (26.45)	64.66 (38.44)	63.77 (20.86)	60.44 (25.13)
TMT errors B	1.36 (5.68)	0.40 (0.91)	0.52 (0.83)	0.15 (0.46)
Gibson's time (ms)	46.02 (15.65)	43.36 (11.77)	44.65 (11.14)	46.58 (12.69)
Gibson's errors	2.50 (2.71)	2.36 (1.87)	3.14 (2.29)	1.81 (2.24)
SWM between errors	10.89 (13.13)	13.44 (15.22)	18.45 (18.28)	13.08 (16.92)
SWM strategy	27.67 (5.51)	28.92 (6.01)	29.72 (5.79)	29.73 (6.97)
RVIP total hits	30.85 (8.44)	31.24 (6.35)	30.79 (9.54)	31.85 (9.07)
RVIP total false alarms	11.48 (25.31)	9.80 (12.65)	22.79 (48.75)	10.46 (13.41)
RVIP mean reaction time for hits (ms)	537.20 (101.61)	518.00 (95.90)	545.62 (115.30)	769.42 (1161.32)

Appendix 6: Ethics approval and volunteer information sheet for studies presented in Chapters 6 & 7

The Joint UCL/UCLH Committees on the Ethics of Human Research: Committee Alpha
The Joint UCL/UCLH Committees on the Ethics of Human Research: Committee A
The National Hospital for Neurology and Neurosurgery and the Institute of Neurology Joint Research Ethics Committee

THE JOINT UCL/ULCH ETHICS COMMITTEE ON HUMAN RESEARCH
COMMITTEE ALPHA

AMENDMENT APPROVAL FORM

Full Title of Study: Weekend and week-day variation in mood and concentration

REC Study No: 98/0173

Drug Company protocol no. (if applicable): N/A

Amendment Number and Date:	Amendment 1, June 2004

The REC has reviewed your amendment.

The REC has no comments.

Your amendment has been:

Approved

The LREC will be notified of the amendment at the next committee meeting on 8 July 2004

Your amendment should be forwarded to appropriate LRECs:

For Information

Signed Ethics Administrator: _____

Print Name:

Date of Report: 18 June 04

The form should be attached to the amendment approval request form sent by you to the REC.

Appendix 6 continued

Sub-Department of Clinical Health Psychology
UNIVERSITY COLLEGE LONDON
GOWER STREET LONDON WC1E 6BT

CONFIDENTIAL

Professor of Psychopharmacology
UCL:
Code from overseas: +44 20
Fax:
e-mail:

VOLUNTEER INFORMATION SHEET

An investigation of week-end and week-day variation in mood and concentration

Investigators: Jatinder Bisla, Rosa Hoshi & Prof H Valerie Curran

Purpose of the study
I am inviting you to take part in a study that will look at how people's mood and concentration varies over the course of a week and whether this is affected by recreational drug use at the week-end.

Background
Although it is commonplace to talk of feeling happier at the week-end compared to the start of the week, it is unclear how people's mood actually changes over 4 days. Week-end use of recreational drugs like alcohol, cannabis or 'ecstasy' can affect people's mood a day or so afterwards but we do not know how these changes fluctuate during the week.

What's involved?
If you agree to take part, you will be asked to fill in some questionnaires about your mood and complete a computer task on a Friday or Saturday night and 4 days later. On day 4 you will also be asked to fill in a drug-use questionnaire. If you have any questions you would like to ask about the study, please do so now.

The data from this study is completely confidential and only the investigators above will have access to it. It will be stored on the principal investigator's computer at UCL but your name will not be recorded on computer and any identifiers to link you to the data will be irretrievably removed.

Please ask the investigator any questions you may have about the study.

You do not have to take part in the study if you do not want to. If you decide to take part, you may withdraw at any time without having to give a reason.

All proposals for research involving human subjects are reviewed by an ethics committee before they can proceed. This proposal was reviewed by the UCL/UCLH Committee on the Ethics of Human Research.

Appendix 7: Mean (SD) self-ratings for ARS, BDI, MRS& SES in male and female ecstasy users and controls (Chapter 6, combined data set)

	Day 0		**Day 4**	
	Ecstasy users	***Controls***	***Ecstasy users***	***Controls***
Restlessness				
Males	65.10 (27.24)	36.43 (24.38)	38.26 (22.83)	30.71 (19.91)
Female	53.06 (31.07)	43.95 (24.44)	33.82 (22.67)	32.79 (19.32)
Total	60.83 (28.92)	39.49 (24.48)	36.69 (22.63)	31.56 (19.53)
Irritability				
Males	12.19 (18.10)	24.55 (19.84)	37.55 (25.76)	28.09 (19.01)
Females	11.41 (12.28)	31.42 (23.35)	37.76 (19.80)	28.33 (22.64)
Total	11.92 (16.15)	27.34 (21.41)	37.63 (23.60)	28.19 (20.37)
Physical tiredness				
Males	22.97 (20.34)	49.20 (22.30)	45.77 (22.11)	43.29 (21.12)
Females	26.06 (20.94)	50.92 (23.17)	56.35 (15.82)	45.29 (21.89)
Total	24.06 (20.38)	49.90 (22.48)	49.52 (20.58)	44.10 (21.26)
Energy				
Males	36.35 (32.14)	48.66 (24.10)	48.58 (19.30)	46.83 (18.60)
Females	35.06 (32.10)	46.08 (21.54)	49.35 (16.42)	41.08 (15.87)
Total	35.90 (31.79)	47.61 (22.94)	48.85 (18.16)	44.49 (17.63)
Dry mouth				
Males	66.52 (29.22)	34.34 (30.29)	17.62 (17.03)	26.86 (25.38)
Females	68.18 (23.61)	31.00 (24.34)	14.35 (15.98)	20.08 (17.65)
Total	67.10 (27.12)	32.98 (27.85)	16.46 (16.57)	24.10 (22.63)
Nausea				
Males	20.87 (20.52)	18.69 (22.00)	6.74 (7.33)	10.69 (15.62)
Females	20.65 (16.20)	14.08 (17.29)	6.76 (9.20)	11.46 (18.78)
Total	20.79 (18.92)	16.81 (20.22)	6.75 (7.94)	11.00 (16.82)
Anxiety				
Males	24.74 (23.47)	26.17 (25.02)	33.61 (26.52)	27.60 (22.20)
Females	15.65 (15.04)	34.67 (24.49)	34.35 (21.17)	32.38 (21.08)
Total	21.52 (21.16)	29.63 (24.95)	33.88 (24.53)	29.54 (21.69)
Sweating				
Males	63.10 (27.49)	26.23 (25.69)	14.68 (15.89)	17.60 (18.72)
Females	44.18 (31.30)	18.38 (17.54)	7.88 (8.59)	5.46 (8.15)
Total	56.40 (29.99)	23.03 (22.89)	12.27 (14.04)	12.66 (16.37)
Blurred vision				
Males	52.29 (22.06)	22.54 (22.91)	11.77 (15.99)	10.23 (17.88)
Females	40.00 (24.12)	26.20 (21.54)	6.82 (10.23)	7.58 (13.09)
Total	47.94 (23.68)	24.03 (22.25)	10.02 (14.30)	9.15 (16.04)